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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

FEBRUARY, 1943

GALL BLADDER DISEASE: ETIOLOGY, DIAGNOSIS AND TREATMENT*

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New and improved methods of determining hepatic function and a clearer view of the physiological activities of the gall bladder have had their effect upon the concept of disease in these organs. Anatomical and physiological abnormalities frequently are seen to precede and serve as a basis upon which disease processes develop. Thus gall stones, cholecystitis, etc., are beginning to be looked upon as organic lesions developed upon an underlying disturbance in structure or function. With

* This includes the following lectures:
1. R. Franklin Carter: "Modern Methods of Diagnosis in Disorders of Gall Bladder Based on Anatomy and Physiology." Presented on February 27, 1942 in the Friday Afternoon Lectures.
2. Thomas H. Russell: "Indications for Surgery and the Surgical Treatment of Diseases of the Gall Bladder." Presented on March 6, 1942 in the Friday Afternoon Lectures.

this knowledge has come the realization of the necessity of dealing with the basic disorder as well as the engrafted pathology, if a complete cure of the condition is to be effected. Such a concept is comparable to the more widely held views relating to diseases of other parts of the gastrointestinal tract, e.g., peptic ulcer and ulcerative colitis.

The concept of gall bladder disease expressed herein has been arrived at through the efforts of the members of a combined clinic for the study and treatment of gall bladder disease established at the New York Post-Graduate Hospital in 1929.* Grouping together the physiological chemist, pathologist and clinician for studies of disease processes casts a new light on previous concepts of management of disease of the liver and gall ducts. Further, the careful sifting of material collected by such a group leads to final conclusions based upon more rational concepts than those arrived at by individual impressions gained from the daily routine of private or individual hospital practice.

The new view does not necessarily change the previous pathological classifications. It adds a new phase, an early dysfunction stage. The failure to eliminate the basic functional disorder by those means directed only toward the engrafted disease complications is emphasized.

The clinic was established for the specific purpose of "determining which patients will be relieved of their symptoms by cholecystectomy." The clinic has been operated by representative members of the various departments. Full time and part time members have participated. Both medical and surgical problems in gall bladder disease have been subjected to a critical analysis under this combination which has been ably assisted by members of the laboratories in physiological chemistry, bacteriology, pathology, and roentgenology.

The classification of gall bladder disease, the mechanism upon which the disease is based, and the special diagnostic signs presented herein are the result of the analysis of the data accumulated in this clinic during the past thirteen years.

From an early study of the data one concept stood out prominently. Continued experience has emphasized and substantiated its importance. Today this concept stands foremost. viz., that gall bladder disease is progressive. Whatever the initiating process, be it functional or organic,

* The clinic was opened under the medical directorship of Herman O. Mosenthal and continued through the directorships of Walter G. Lough and Irving S. Wright; under the surgical directorship of John F. Erdmann and continued through the directorships of Charles Gordon Heyd and Thomas H. Russell. J. Russell Twiss and Carl H. Greene have been the active directors in medicine and R. Franklin Carter the active director in surgery.

time adds factors such as gall bladder stones, infection, obstruction and obliteration of the gall bladder. Then the influence of the initiating factor often begins to exert its influence directly upon the common duct. Here again, the process may be either functional or organic, with the factors of common duct stones, infection, obstruction, cirrhosis of the liver and spleen occurring in the course of time.

The second fact realized, no less important than the first, was the necessity of determining the actual underlying cause of the disease process, i.e., the initiating factor. The importance of understanding the mechanism setting the disease process in motion lies in the fact that treatment of the organic lesion such as removal of gall bladder stones and even the gall bladder itself may not result in the complete eradication of the initiating factor. This will be seen in the section dealing with hypertonic dyssynergia. Cholecystectomy fails to relieve the patient's symptoms when the sphincter of Oddi is the actual site of the difficulty. The best explanation offered for the pre-operative pain in this type of gall bladder disorder is that the nerve endings in the wall of the gall bladder are excited by a pressure stimulus developed within the cavity. Two forces are at work; the resistance of the spastic sphincter of Oddi to the emptying of the gall bladder and the exertion of the gall bladder musculature to overcome this resistance. The opposition of these two forces results in an increase of tone in the gall bladder to the point of tonic contraction. Colic mechanisms of this nature are seen in other hollow viscera, e.g., urethral obstruction. Postoperatively the pain is due to the increased intraductal pressure resulting from the sphincter spasm. In contrast, cholecystectomy may be expected to cure the disease process when it is limited solely to the gall bladder itself, as will be shown in the section on anatomical causes disturbing the filling and emptying mechanism of the gall bladder.

Still another fact of importance was the necessity of determining pre-operatively the presence or absence of actual infection in the gall bladder. This will be discussed in the section dealing with infectious cholecystitis.

The general routine in use by the clinic is as follows: After a history and physical examination, a blood specimen is taken for the determination of cholesterol and cholesterol esters. The normal total cholesterol in the blood varies from 160 to 220 mgm. per cent. The esters range from 40 to 60 per cent of this total if liver function is normal. The icteric

index and Van den Bergh tests are also done. The cholesterol-ester ratio is not the sole liver function test used. In patients in whom liver function impairment is suspected, other recognized tests are also utilized, e.g., the cephalin flocculation test, bromsulphalein test, etc.

A duodenal drainage is then performed with sterile technique. Four specimens are obtained. First, a specimen of the gastric juice on which the total acidity and free hydrochloric acid are determined. When indicated, a fractional test of gastric secretion is performed. Next, a specimen of the duodenal contents is obtained before any type of stimulant has been administered. This is referred to as the "D" specimen. After this, one ounce of 25 per cent magnesium sulphate is introduced through the tube. The specimen obtained is referred to as the "M" specimen and is of a darker amber color than the "D." Lastly, one ounce of olive oil is introduced into the duodenum. This stimulates the gall bladder to contract, and under normal circumstances, dark concentrated bile, referred to as the "O" specimen, is obtained. The obtaining of specimens as described above constitutes a *normal* response to duodenal drainage. Variations from this pattern constitute an *abnormal* response, e.g., the failure to obtain concentrated bile after stimulation with olive oil in a patient who has an intact gall bladder. Patients who respond in a similar manner to several drainages are said to have a *regular* response. Those who differ from drainage to drainage, e.g., concentrated bile one time and not the next, etc. are said to have an *irregular* response. Each specimen of bile is examined microscopically for evidence of stasis, i.e., the presence of crystals, either cholesterol or calcium bilirubinate. Normally, no crystals should be found, or at the most, an occasional crystal per 10 low power fields. Specimens are sent for bacteriological culture, and under normal conditions, should be negative. In special cases, the pancreatic ferments in the bile specimens are determined. A roentgenogram series of the gall bladder is taken using a double dose of dye given orally.

Disease or dysfunction of the gall bladder and the biliary tract manifest themselves either in the history, liver function test, duodenal drainage, or roentgenogram. By integrating these findings, patients are classified into various etiological categories prior to initiation of therapy. If surgery is indicated, cultures are made of the operative specimens. A chemical analysis of the bile is also done. Thus, the pre-operative classification is checked by the operative findings.

Etiology (Initiating Factors)

Patients may be divided into three groups:

1. Those with disorders resulting in a disturbance of the filling and emptying mechanism of the gall bladder.

2. Those with disorders resulting in interference with the concentrating mechanism of the gall bladder.

3. Those with diseases of the blood and metabolism which manifest themselves in disorders in the biliary tract.

In the ensuing discussion of the various etiological factors of gall bladder disease, it has been our aim to seek out the *cause* by which each factor produces its *effect*. *Treatment* is directed wherever possible at removing both the *cause* and *effect*. The *prognosis* in any group depends on the success of the available treatment in achieving this dual purpose. The particular clinical and laboratory findings pertaining to each group are mentioned. The consideration of each group in such a manner, enables the comparison of the various etiological factors as regards mechanism, treatment and prognosis.

Disorders Affecting Filling and Emptying Mechanism

Disorders resulting in disturbances in the filling and emptying mechanism of the gall bladder are listed in Table I. The causes of these disturbances may be anatomical or physiological. The anatomical causes may be subdivided into external and internal causes. The external causes may be either congenital or acquired while the internal are all congenital. The physiological causes of disturbance in the filling and emptying mechanism are the result of dyssynergia, known also as dyskinesia. There are two types of dyssynergia, the hypertonic and the hypotonic. The site of the basic disorder in the former is at the sphincter of Oddi, and in the latter, in the gall bladder wall.

Anatomical Causes (Mechanical)

The changes in structure found to initiate the process of gall bladder disease by interference with the outflow of bile are present, and exert their influence throughout the course of the disease. Their significance may be lost and is apt to be overlooked in the advanced stages of the disease unless one be intent upon seeking the initiating fac-

TABLE I

DISORDERS RESULTING IN DISTURBANCES IN FILLING AND EMPTYING MECHANISM OF GALL BLADDER

A. ANATOMICAL CAUSES (MECHANICAL)

1. *External—Congenital or Acquired*

(a) Adhesions—Congenital or Inflammatory

(b) Abnormal Cystic Artery

(c) Pancreatic Inflammation—Edema, Fibrosis with Common Duct Involvement

(d) Tumors of Pancreas and Extra-Hepatic Bile Ducts

2. *Internal—All Congenital*

(a) Convoluted Cystic Duct—Valve of Heister Obstruction

(b) Septa—"Phrygian Cap"

B. PHYSIOLOGICAL CAUSES (FUNCTIONAL)

1. *Hypertonic Dyssynergia*

2. *Hypotonic Dyssynergia*

tors. A knowledge of their existence and detection is important in selecting a surgical procedure to deal with the entire scope of the disease as well as in making a correct prognosis regarding the ability of the chosen procedure to completely eradicate the disease process, or merely to remove the superadded complications of the irremovable basic disorder.

EXTERNAL

a. *Adhesions*

As every surgeon knows, adhesions are very frequent in the upper abdomen. They can seldom be shown to be the positive cause of gall

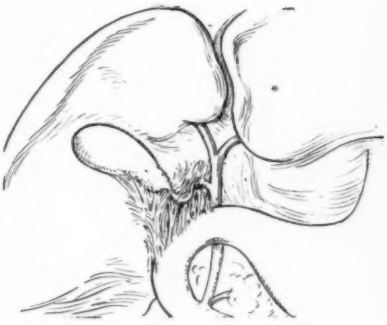


Fig. 1

Fig. 2

bladder disturbance but are considered to be the initiating factor for gall bladder disease in approximately 10 per cent of patients in this group. Their formation may be congenital as in an abnormal development and persistence of the cystic duodenal fold, or acquired from inflammation in adjacent structures such as duodenal ulcer or duodenitis. The acquired adhesions when present offer an additional direct route for the lymphatic spread of infection to the gall bladder.

The symptoms in a patient with adhesions are irregular attacks of colicky pain. The mechanism of these attacks of pain is explained as being due to the development of a pressure stimulus to the nerve endings in the gall bladder wall by the exertion of emptying bile through the partial obstruction offered by the distorted cystic duct (Fig. 1). In sensitive patients, an expression of a burning or tugging sensation in the right upper quadrant is a characteristic complaint. The characteristic roentgenograms show a small, densely concentrated gall bladder shadow with no visualization of the cystic duct (Fig. 2). The duodenal drainage is not distinctive.

Cholecystectomy results in the complete cure of the patient's symptoms. This is to be expected by reason of the fact that the scope of the disorder is entirely contained in the gall bladder. If, however, operation is not performed and the condition persists, there occurs a pathological stasis of bile. Precipitation of crystals, usually cholesterol, occurs and the formation of cholesterol stones results (Fig. 3). In this stage and for as long as the stones remain free in the gall bladder cavity, the

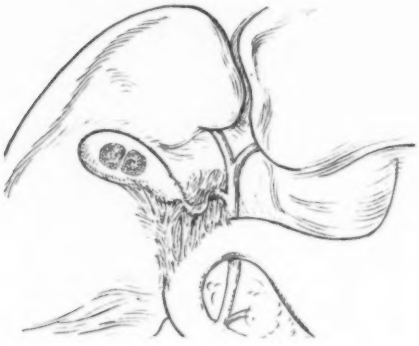


Fig. 3

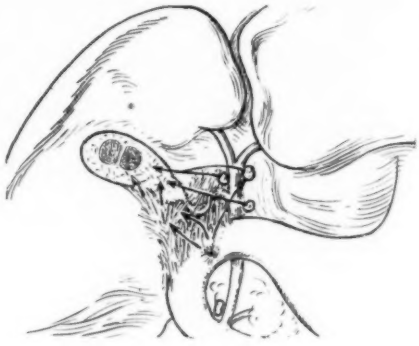


Fig. 4

symptoms are the same as in the pre-stone stage. A roentgenogram shows normal concentration and negative shadows if no infection intervenes.

Should infection be superimposed on the gall bladder in this stage by spread, for example, from a concomitant duodenal ulcer (Fig. 4), then calcium bilirubinate is laid down on the cholesterol stone or stones and the mixed type of stone results, giving positive shadows in the roentgenogram. If the mucosa becomes inflamed, the concentrating function is affected and there is also faint or lack of concentration of dye as shown by roentgenogram. The short periods of discomfort are replaced by longer periods of a dull aching pain in the right upper quadrant. The course of the attacks begins mildly, increases in severity and gradually subsides, the whole extending over a period of four to ten days. Typical duodenal drainage shows no concentrated bile, crystalline sediment, and if infection is active, a positive culture. At this stage, while the infection is still limited to the gall bladder, cholecystectomy will cure the patient of symptoms and terminate the disease.

If, however, surgery is not done, sooner or later an engagement of the stone in the outlet of the gall bladder occurs with the development of a hydrops or empyema. When there are repeated attacks of empyema of the gall bladder, seepage of infected bile into the common duct occurs. Cholecystectomy at this point still cures the patient, and the uncomplicated contamination of the common duct will clear up. The outstanding findings in this stage are a palpable mass in the right upper quadrant and non-visualization of the gall bladder by roentgenography.

If, however, the gall bladder is not removed and the drainage of infectious material into the common duct persists, the infection becomes entrenched in the sacculi in the wall of the common duct. When the patient has reached this stage, simple cholecystectomy, although removing the obstructed gall bladder and with it the initiating cause of the disease, i.e., adhesions around the cystic duct, will not clear the common duct sacculi of the infection. The neglect of surgical treatment permits the residual nesting of organisms in the common duct sacculi to act as a focus of infection. Chronic and recurring acute attacks of choledochitis, i.e., "Charcot's fever" occur. A patient who has reached this stage requires medical treatment after cholecystectomy, viz., frequent duodenal drainages, bile salts, antispasmodics, etc. This is directed toward insuring a free flowing current of bile passing through the common duct to prevent stasis and wash out detritus. If this is not done, the patient is confronted with the danger of developing a common duct stone. Choledochotomy with removal of the stone is then required. Failure to remove the stone subjects the patient to biliary obstruction and possibly pancreatitis. Thus, the surgery in each stage becomes progressively more complicated. Fortunately in this category of gall bladder disease, patients tend to appear early for surgery and the terminal stages of persistent common duct infection and common duct stone are rarely encountered.

Summary: The prognosis for complete cure of the patient's symptoms and eradication of the disease process is reduced as time goes on. The basic initiating factor of adhesions around the cystic duct is removed by cholecystectomy at any time. The acquired factor of infection is eradicated by cholecystectomy up to the point when chronic involvement of the common duct sacculi occurs. At this stage more complicated operative procedures, e.g., cholodochotomy and "by-pass" operations between the common duct and duodenum, become necessary. Even these usually fail to permanently eradicate the infection once it has become firmly entrenched. Various medical procedures have proved disappointing in this regard as well. The subject will be discussed more fully in the section devoted to infectious cholecystitis.

The progressive nature of gall bladder disease; the complications superadded with the passage of time as described in this section will be seen to apply to the various other types of gall bladder disease to be discussed even though the basic initiating factors are different.

b. *Abnormal Cystic Artery*

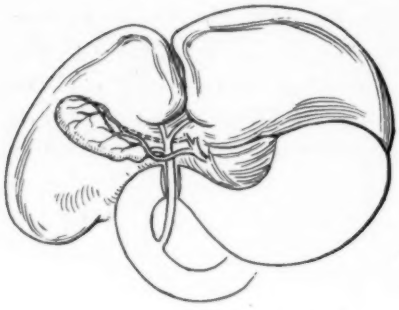


Fig. 5

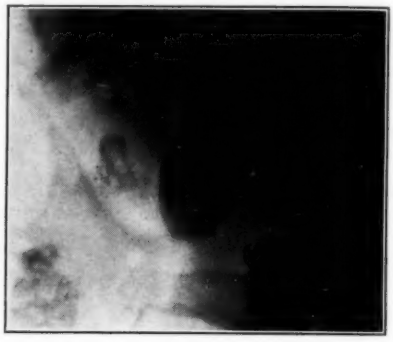


Fig. 6

PRE-STONE STAGE

MECHANISM

Cause (Fig. 5)

Any origin of cystic artery that necessitates its crossing the cystic duct to reach margin of gall bladder.

Effect

1. Compression of cystic duct.
2. Pain from pressure stimulus developed from increased effort of emptying against a partial compression of cystic duct.

TREATMENT

Cholecystectomy.

RESULT

Cure–initiating factor eradicated.

PROGNOSIS

Physiological effect of cholecystectomy is a moderate dilatation of common duct, normal process.

SPECIAL DIAGNOSTIC POINTS

History

1. Thought to be one of causes for cyclic vomiting, migraine, sensitive stomach, etc., occurring in early life.
2. Intermittent attacks of gall bladder colic. Prone to appear after loss of weight and liver ptosis. Amyl nitrite – no relief of symptoms.

Roentgenogram (Fig. 6)

No enlargement of gall bladder. Distinct concentration of dye. Markedly delayed emptying after fatty meal.

Duodenal Drainage

Small volumes of concentrated bile in response to stimulation. Crystalline sediment–cholesterol. Culture of duodenal specimen of bile negative.

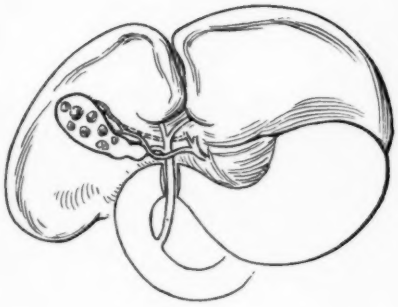


Fig. 7

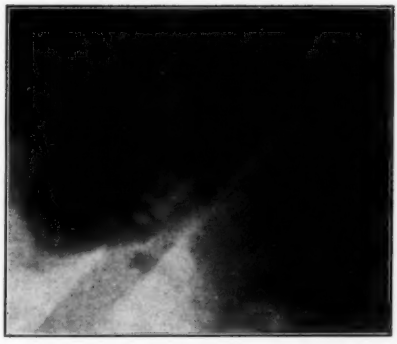


Fig. 8

STONE STAGE

MECHANISM

Effect—continued

1. Continuous process bile stasis. Uniform precipitation cholesterol crystals. Result large single or multiple stones (same family). (Fig. 7.)
2. Pain as in pre-stone stage.

TREATMENT

Cholecystectomy.

RESULT

Cure.

PROGNOSIS

Physiological dilatation of common duct.

SPECIAL DIAGNOSTIC POINTS

History

Same as pre-stone stage.

Physical Signs

Negative.

Roentgenogram (Fig. 8)

Normal concentration. No enlargement. Delayed emptying. Negative stone shadow.

Duodenal Drainage

Normal response—small quantity. Crystalline sediment—cholesterol. Culture of bile—negative.

Summary: Cholecystectomy includes the entire disease producing factor and resulting changes up to this point of development.

Patients in whom the condition is not diagnosed, and those refusing operation during one of the two stages described above will in time develop the succeeding stages of gall bladder diseases. Usually, however, cholecystectomy is done early.

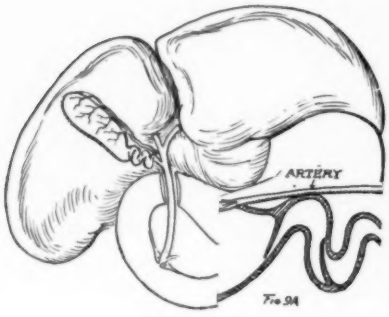
c. *Pancreatic Inflammation*

d. Tumors of Pancreas and Extra-Hepatic Bile Ducts

Causes "c" and "d" are included in Table I for completeness. While it is true that they interfere with the emptying mechanism of the gall bladder, such a disturbance is of minor importance compared with the primary condition.

INTERNAL

a. *Convoluted Cystic Duct—Valve of Heister Obstruction*



Figs. 9-9A

Fig. 10

PRE-STONE STAGE

MECHANISM

Cause

Ruffling of the cystic duct, the reason for which is not clearly understood. Can be easily demonstrated after removal and longitudinal section of specimen. The cystic artery will then be seen to pursue a straight course. The cystic duct is convoluted suggesting the accommodation of an elongated cystic duct to a shortened cystic artery. (Fig. 9.)

Effect

1. Pain resulting from a pressure stimulus developed by the gall bladder attempting to empty against a partial obstruction of the cystic duct due to a "foot valve" action of the valves of Heister. (Fig. 9A.)
2. Tendency in many instances to tubular enlargement of the gall bladder similar to that seen in hypertonic dyssynergia.

TREATMENT—Cholecystectomy.

PROGNOSIS—Cure.

SPECIAL DIAGNOSTIC POINTS

History

1. Tendency to occur in individuals bordering on the ulcer type.
2. Irregular attacks of pain in R. U. Q. Severe colicky pain associated with eating heavy meals after periods of fasting.
   Amyl nitrite – no relief of symptoms.
3. Any condition in which there is prolonged storage of bile in the gall bladder predisposes to an attack, e.g., periods of starvation. Association with gastrointestinal upsets.

Roentgenogram

Dense concentration and frequently visible tortuous cystic duct. Delayed emptying (Fig. 10).

Duodenal Drainage

Irregular response. Crystalline sediment when dark bile is obtained. Culture of duodenal specimen of bile negative.

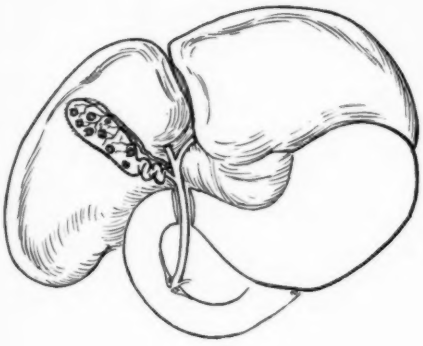


Fig. 11

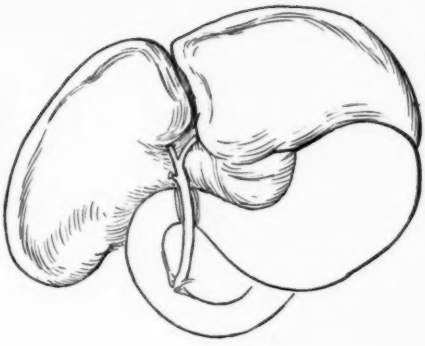


Fig. 12

STONE STAGE

MECHANISM

Effect—continued

1. Bile stasis—all elements. Precipitation of crystals and stone formation. (Fig. 11.)
2. Pain as pre-stone stage.
3. Severe lancinating pain if stone becomes engaged in cystic duct.

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure. Physiological dilatation of common duct. (Fig. 12.)

SPECIAL DIAGNOSTIC POINTS

History

Irregular attacks of colicky pain, nausea and vomiting.

Amyl nitrite—no relief of symptoms.

Roentgenogram

Normal concentration of dye with negative stone shadows in non-obstructive cases. No visualization if gall bladder obstructed at time by stone in the cystic duct.

Duodenal Drainage

Irregular response to stimulation (difficulty in drainage). Crystalline sediment in dark bile.

Culture of duodenal specimen of bile negative.

Summary: Cholecystectomy will eradicate the causal mechanism and remove the effect of the condition. Neglect to remove the gall bladder will be followed by a continuation of the process. Superimposed infection or mechanical obstruction by stone leads to the final destruction of the gall bladder without the assistance of the basic factor. Infection can then spread to involve the common duct and result in common duct stone, obstruction and biliary cirrhosis. However, failure to relieve symptoms by medical means as a rule induces early operation.

b. *Septa–Phrygian Cap*

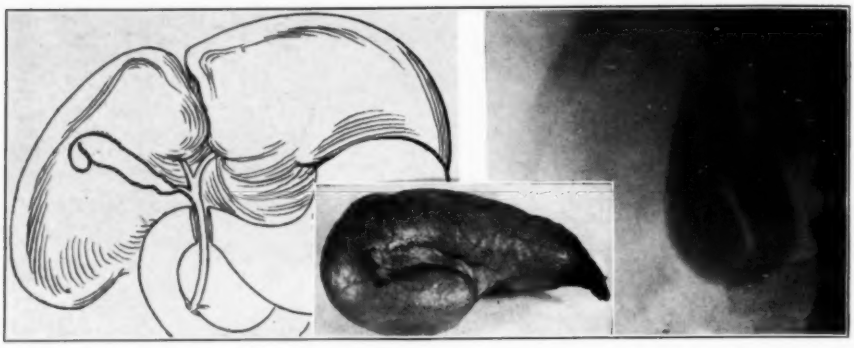


Fig. 13 Fig. 13A Fig. 14

PRE-STONE STAGE

MECHANISM

Cause (Fig. 13, 13A)

Congenital septum interposed at some point in the cavity of the gall bladder, usually the fundus. Probably due to incomplete vacuolization of the cavity. (General incidence 6 per cent.)

Effect

1. Partial obstruction of the distal cavity.
2. Pain from pressure stimulus developed within the distal segment of the gall bladder attempting to empty against obstruction of the interposed septum.

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure. Physiological dilatation of the common duct.

SPECIAL DIAGNOSTIC POINTS

History

1. No specific symptoms directly attributable to deformity.
2. Intermittent periods of pain and distress. Associated with eating heavy foods.
   Amyl nitrite – no relief of symptoms.

Roentgenogram (Fig. 14)

Normal visualization of body and fundus. Visualization of cap. Delayed emptying of cap. Frequently mistaken for extraneous adhesions.

Duodenal Drainage

Normal response. Crystalline sediment–cholesterol frequently present. Culture of duodenal specimen of bile negative.

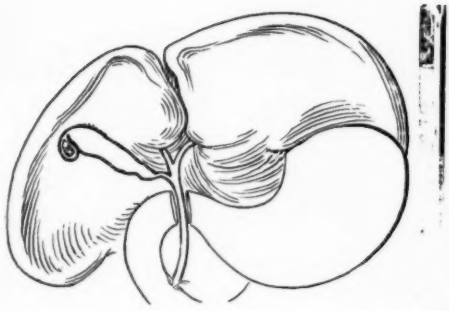


Fig. 15

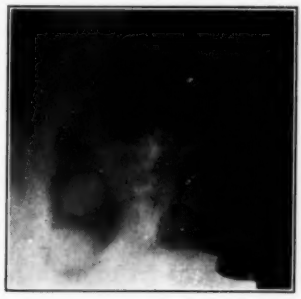


Fig. 16

STONE STAGE

MECHANISM

Effect—continued

1. Bile stasis—all elements. Precipitation of crystals and mixed stone formation in the cap. (Fig. 15.)
2. Complete obstruction. Stone engaged in aperture between cap and fundus.

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure.

SPECIAL DIAGNOSTIC POINTS

History

Continuous distress of distention. Intermittent attacks of pain due to engagement of stone in the narrowed orifice of the distal segment.

Amyl nitrite—no relief of symptoms.

Roentgenogram (Fig. 16)

Normal concentration gall bladder. Delayed emptying and no visualization of cap. Possible negative stone shadow outside gall bladder shadow.

Duodenal Drainage

Normal response. Crystalline sediment – cholesterol – not distinctive. Culture of duodenal specimen of bile negative.

Summary: Whatever stage the disease process may have reached in patients in this group at the time of operation, that found in the cap appears to be most advanced. These findings suggest a progressive spread of the disease process from the cap to the gall bladder and then to the common duct. It resembles the course seen to occur in the gall bladder. Many patients are operated upon during an attack of acute abscess of the cap. Few progress to advanced common duct disease.

Physiological Causes (Functional)

There exists a difference of opinion as to the existence and importance of functional disorders as an initiating factor in the development of biliary tract disease. In the Gall Bladder Clinic at the Post-Graduate Hospital approximately two-thirds of all patients with gall bladder disease are believed to have had a disturbance in the filling and emptying mechanism of the gall bladder in the primary stage. A final analysis, especially that of follow-up findings shows the majority of patients to have had dyssynergia.

The functional disorder interfering with the filling and emptying mechanism of the gall bladder may be of two types. First, that due to an increased resistance to the flow of bile through the sphincter of Oddi –hypertonic dyssynergia, and second, that due to the diminished contractility of the gall bladder wall–hypotonic dyssynergia.

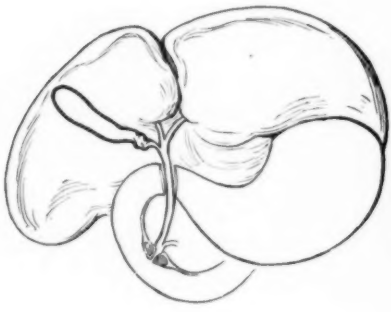


Fig. 17

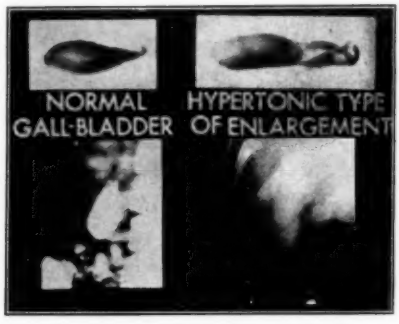


Fig. 18

Hypertonic Dyssynergia

The site of the primary dysfunction in hypertonic dyssynergia lies at the sphincter of Oddi at the lower end of the common duct (Fig. 17). There the increase in tone and hypertrophy is associated with one or other of two etiological factors. First, along with gastric hyperacidity and its associated duodenitis and papillitis. Second, as the result of a reflex spasm of the sphincter. The reflex may be from a distant primary site such as a diseased appendix or from the central nervous system. Whichever the factor concerned, the result is similar, namely, an increased resistance to the emptying of bile into the duodenum. The effect of this is a compensatory enlargement of the gall bladder which is

called upon to store larger quantities of bile. Hypertrophy of the gall bladder wall occurs as a result of the increased effort required to expel the bile. Pain is experienced from the development of a pressure stimulus to the nerve endings in the gall bladder wall due to these abnormal contractions, and a stasis of bile occurs due to the incomplete emptying of the gall bladder.

The patient experiences attacks of colicky pain in the right upper abdomen or epigastrium. Relief of the pain instantly after the inhalation of amyl nitrite is usually one of the characteristic features of this type of gall bladder disease. The roentgenogram shows normal concentration with delayed evacuation. The gall bladder is enlarged and tubular. The walls are thickened and hypertrophied (Fig. 18).

Cholecystectomy is contra-indicated in this type of non-calculous gall bladder disease for two reasons: first, the primary disturbance is not in the gall bladder. Secondly, if the gall bladder is removed, the pressure-regulating mechanism of the biliary tract goes with it. With continued dysfunction of the sphincter, therefore, the pressure within the common duct is greatly increased with a recurrence of symptoms. This type of patient requires medical treatment directed toward the cause of spasm of the sphincter of Oddi.

In the presence of duodenitis associated with hyperchlorhydria, a bland diet with antacids and antispasmodics are prescribed. If the spasm is believed to be reflex in nature, a diligent search is made for any focus of irritation especially in the abdomen. The psychic background of the patient is taken into consideration and often the assistance of the social worker is required for the proper approach to the cause of the condition. Unsuitable home conditions, unemployment and financial worries are all potent factors in the production of this type of dyssynergia.

Failure for such a patient to receive proper medical treatment leads to pathological bile stasis in the gall bladder. This is accompanied by sedimentation, crystallization and the formation of stones (Fig. 19). The symptoms and signs of increased pressure within the gall bladder continue as in the pre-stone stage. The characteristic roentgenogram shows stones in a normally concentrating and enlarged gall bladder (Fig. 20). Duodenal drainage shows irregular response to olive oil with crystalline sediment on microscopic examination. Culture of the bile specimen is sterile at this stage before the advent of infectious cholecystitis. It is customary to advise cholecystectomy in this stage of hypertonic dys-

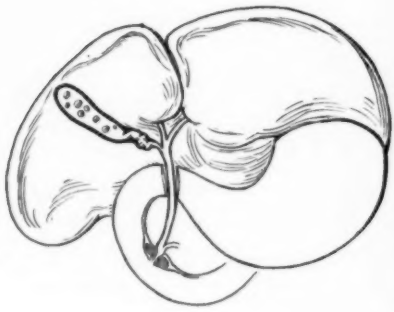


Fig. 19

Fig. 20

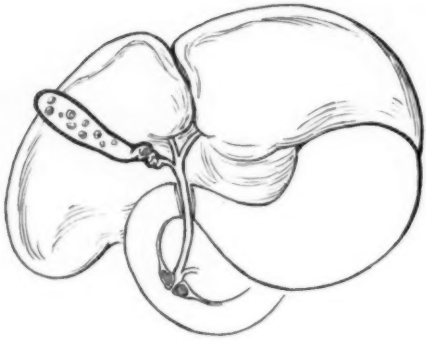


Fig. 21

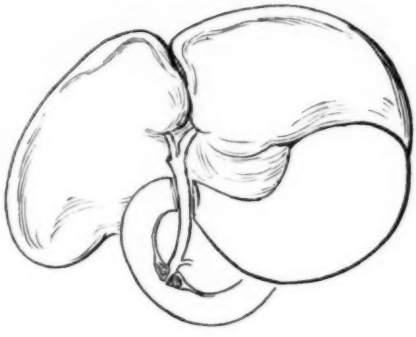


Fig. 22

synergia with stones. This is done not with the intention of removing the cause of the disease process and of curing the patient's symptoms, but rather to prevent the impaction of a stone in the cystic duct. It must be emphasized that patients in this group are not cured by cholecystectomy which eradicates only the result of the disease mechanism. The impaired bile duct mechanism remains beyond the scope of cholecystectomy.

If the patient does not present himself for attention while in the free stone stage, one of the stones is likely to become impacted in the cystic duct. This results in a temporary hydrops of the gall bladder (Fig. 21). In the absence of infection, the gall bladder bile becomes absorbed. In this stage there are severe attacks of colicky pain in the right upper quadrant which respond irregularly to amyl nitrite but are

relieved somewhat by morphine. This is helpful in determining the stage of development of the disease in a patient in whom amyl nitrite has relieved previous attacks. Roentgenography shows concentration of dye before permanent engagement of the stone occurs in the cystic duct, and no visualization afterwards. Cholecystectomy, while removing the non-functioning gall bladder, still does not cure the patient's underlying pathology. After cholecystectomy (Fig. 22), the sphincter resistance to the flow of bile from the common duct into the duodenum is still increased. Under the circumstances, the intraductal pressure increases and the bile ducts dilate beyond the usual physiological extent following cholecystectomy. In an effort to accommodate the bile secreted by the liver which cannot freely enter the duodenum, the bile ducts concentrate the bile. The concentration, however, never equals that of the gall bladder. Such concentrated bile, when obtained after cholecystectomy, is evidence of sphincter spasm and stasis in the common duct. Continued spasm of the sphincter of Oddi leads to overdistention of the common duct and pain which is chiefly located in the epigastrium. To prevent symptoms after cholecystectomy, the cause of the sphincter spasm must be located and treated medically. Surgical treatment by cutting the sphincter from within has been attempted but not established as a procedure to be undertaken generally. In severe instances accompanied by recurrent jaundice, a "by-pass" choledochoduodenostomy may become necessary.

In a non-infected, obstructed, hypertonic gall bladder, absorption of water and bile elements by the mucous membrane does not cease. If the cystic duct obstruction remains for any length of time, the bile in the gall bladder at the time of the obstruction will be absorbed and the gall bladder will contract down around the stones. If the stones are small, and in this type of dyssynergia they usually are, one or more stones may be forced through the dilated cystic duct into the common duct (Fig. 23). In the absence of jaundice, such stones are often overlooked at operation. A contracted gall bladder containing small stones associated with a dilated cystic duct is an indication for exploration of the common duct (Fig. 24). Search for and recognition of this fact should prevent many secondary operations for removal of overlooked stones from the common duct. Patients with overlooked stones in the common duct (Fig. 25) constitute a difficult diagnostic problem. In the absence of jaundice, it is impossible with our present means of

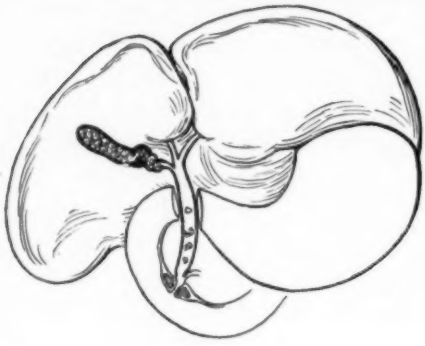


Fig. 23

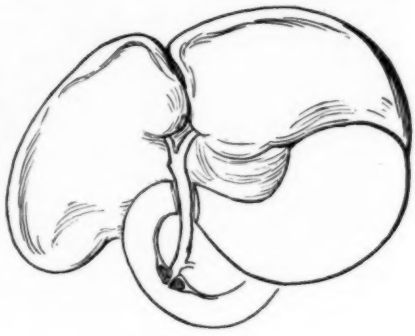


Fig. 24

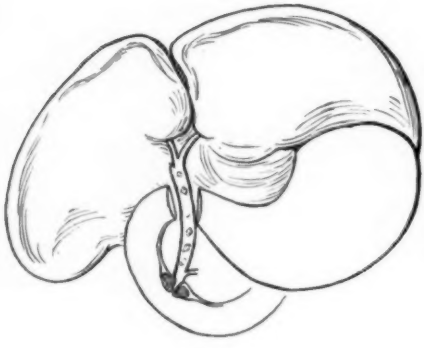


Fig. 25

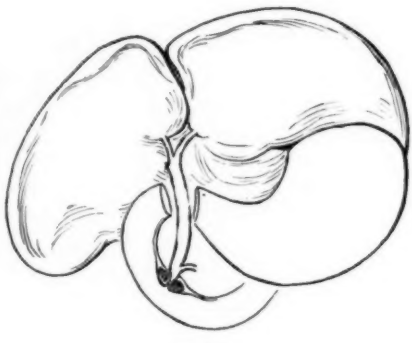


Fig. 26

diagnosis to be sure that a patient's symptoms after cholecystectomy which appear resistant to medical treatment are not due to a common duct stone. On the other hand, choledochotomy is inadvisable as a routine procedure in all post-cholecystectomy cases with persistent pain. At one time the finding of a moderate number of crystals in duodenal drainage specimens was thought to be an indication of stones remaining in the common duct. Such an attitude resulted in several patients having an exploratory choledochotomy in whom no stones were found. All such cases should first be subjected to a strict, controlled, medical regime to rule out the possibility of the symptoms being due to uncomplicated sphincter spasm and its train of events. At the Gall Bladder Clinic the policy that has met with the greatest success is to keep the patient under observation and refrain from secondary common duct operations until jaundice appears. Removal of the common duct stones

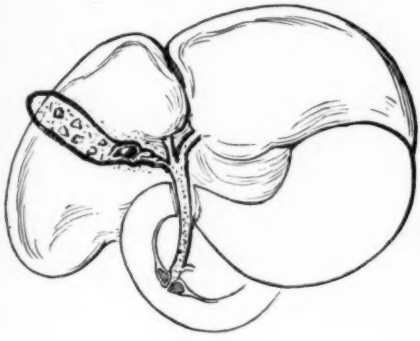


Fig. 27

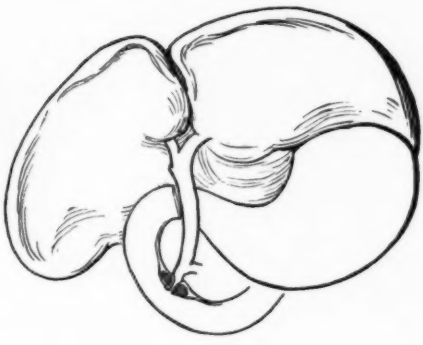


Fig. 28

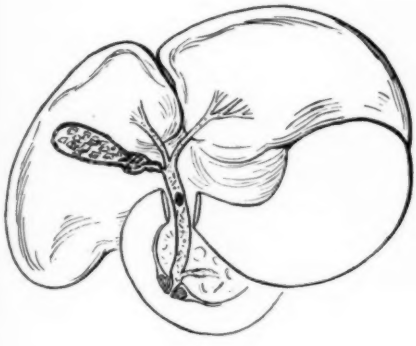


Fig. 29

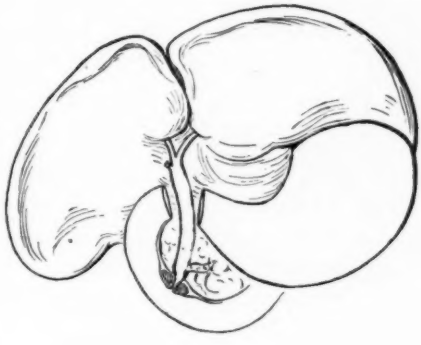


Fig. 30

(Fig. 26) must still be followed by medical treatment of the underlying sphincter spasm.

Infection is occasionally superimposed on one of the stages of hypertonic dyssynergia discussed above. If infection occurs in the stage of cystic duct obstruction, then empyema of the gall bladder results (Fig. 27). The route of the infection may either be by the blood stream, through the liver, or ascending through the duodenum. The characteristic attacks of colicky pain change to prolonged attacks of dull pain and tenderness in the right upper quadrant accompanied by fever and leukocytosis. The outstanding findings on physical examination are a palpable gall bladder like mass, tenderness and rigidity in the right upper quadrant. Roentgenography or duodenal drainage are not indicated

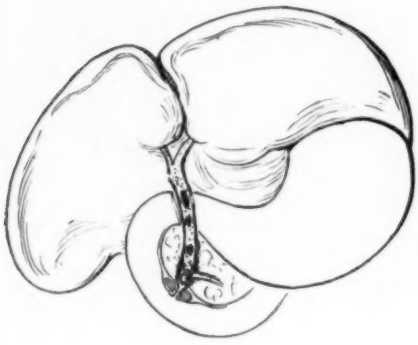


Fig. 31

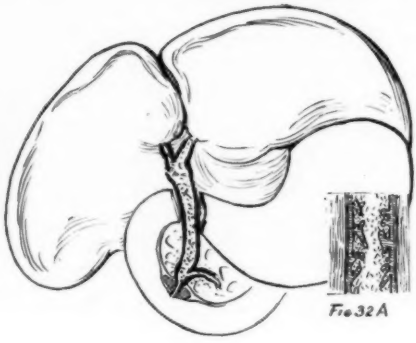


Fig. 32A

in the presence of a definite and characteristic gall bladder mass. Such a clinical picture is sufficient reason for an abdominal exploration. In those with signs of acute cholecystitis and no mass, roentgenography and duodenal drainage are indicated since the gall bladder is fibrotic and not liable to rupture during the investigation. Seepage of the infected bile occurs into the common duct which is contaminated by the offending organisms. A mild cholangitis may occur with slight fever and chills. However, removal of the gall bladder at this stage usually results in the clearing up of the superficial contamination of the common duct (Fig. 28).

In this stage, as in the non-infected, obstructed gall bladder, a stone may become extruded into the common duct. This is most apt to be found after the gall bladder, subjected to several attacks of a low-grade inflammatory nature, becomes thickened and contracted (Fig. 29). Recognition of the common duct stone at operation with its removal usually leads to the clearing up of the infection in the common duct (Fig. 30). The theory that an obstructed gall bladder or cystic duct might reflexly cause a common duct sphincter spasm was held for some time. Experience has shown this concept usually to be false as the spasm persists after removal of the gall bladder.

It should be stressed that medical treatment of the underlying tonic sphincter is important in these patients not only for the relief of their symptoms but to insure a free flow of bile through the common duct to clear out the organisms before they become firmly entrenched. If, however, common duct stones are overlooked (Fig. 31), then the cho-

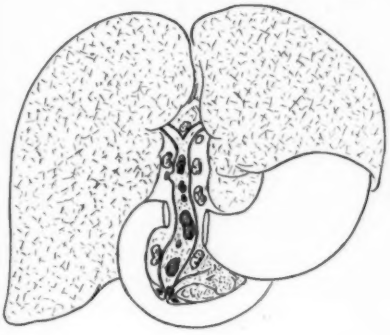


Fig. 32B

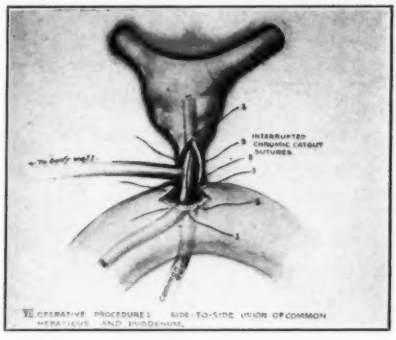


Fig. 32C

langitis will persist and in time the infection will become firmly entrenched in the sacculi of the wall of the common duct (Fig. 32 A). In addition, should the pancreatic duct unite with the common duct above the sphincter before entrance into the duodenum, the impaction of one of the common duct stones at the sphincter of Oddi exposes the patient to a reflux of infected bile into the pancreas with subsequent pancreatitis. Once the sacculi of the common duct have become a residual focus of infection, removal of the common duct stones will not usually be followed by eradication of the infection (Fig. 32). The patient at this stage has a chronic cholangitis. Periodic attacks of chills and fever with jaundice occur if the sphincter is not kept relaxed by medical treatment.

Ultimately the infection extends from the common duct up to the small bile canaliculi and then to the liver parenchyma itself—biliary cirrhosis. The involved liver is enlarged and hard; the common duct markedly dilated. Common duct stones are very apt to be reformed under these conditions in the common duct (Fig. 32B). To insure a free flow of bile and remove the pressure from the liver in this terminal stage of gall bladder disease, one may have to resort to a choledochoduodenostomy (Fig. 32C). Thus, what started out as a functional disorder of the biliary tract may over the span of years ultimately result in advanced organic disease. The entire course of gall bladder disease ending with biliary and splenic cirrhosis with portal obstruction has been observed in a 31 year old patient in our clinic. During the course of eight years of the disease there were performed a cholecystostomy with removal

of stones, cholecystectomy, and four operations for removal of common duct stones. The patient succumbed to gas bacillus bacteriemia following a fifth operation for removal of a reformed common duct stone. During the last operation a "by-pass" was made between the duodenum and common duct for the relief of the still existent dyssynergia and for permanent drainage of the incurable B. Welchi and B. coli infection of the common duct. Positive cultures of these organisms were found in the common duct at the last operation.

HYPOTONIC DYSSYNERGIA

The other type of dyskinesia which interferes with the filling and emptying mechanism of the gall bladder is the hypotonic type (Fig. 33). Here the site of the dysfunction lies not in the sphincter of Oddi, but in the gall bladder wall. It is what has been termed the "lazy gall bladder." Roentgenography shows a large, pear-shaped gall bladder which concentrates the dye with delayed evacuation after a fatty meal. The wall of the gall bladder in contrast to the hypertonic type, is thinned out and atrophic (Fig. 34).

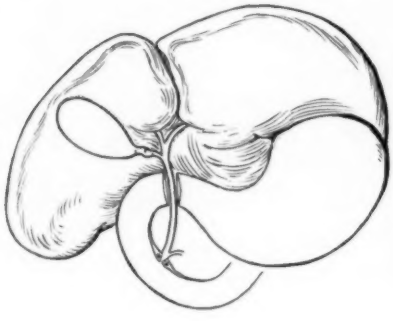


Fig. 33

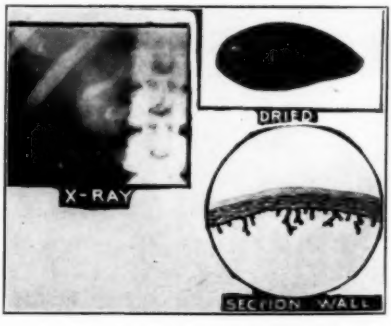


Fig. 34

The patient often shows other evidence of hypotonia such as a low basal metabolic rate, low or absent free hydrochloric acid in the gastric juice, hypercholesterolemia, etc. These patients do not have colicky pain since the tone of the gall bladder wall and its contractions are not sufficient to increase the intravesical pressure to the point of developing an actual pain stimulus. These patients complain of mild discomfort in the upper quadrant associated with gastric irritability, belching and dis-

tention after meals. Because of the relative mildness of the symptoms, these individuals are infrequently seen in the Gall Bladder Clinic in this primary or pre-stone stage. Frequently they are treated in the Colon or Gastro-intestinal Clinic as in the early stages the stomach and colon show a similar tendency for dysfunction. The statement is frequently made that a physician's special interest in any of the fields into which these patients can be included is the controlling factor in the interpretation and treatment. A well executed routine of medical treatment has been credited with prevention of stones, improvement of gall bladder function and relief of symptoms in patients with hypotonic dyskinesia and bile stasis who have been followed continuously over a period of ten years.

The general incidence of this type of dyssynergia is much greater than is revealed in the analysis of the charts of patients coming to the Gall Bladder Clinic prior to stone formation. A better indication of the true incidence of hypotonic and hypertonic dyssynergia is found in a comparison of patients in the two groups in whom there has occurred stones in a gall bladder that is still functioning. Proper classifications upon the basis of all the findings in a large group of patients shows the relative occurrence to be about equal in the two types of dyssynergia. The laboratory work-up in such individuals shows normal liver function and usually hypercholesterolemia. Roentgenography shows concentration of the dye with delayed evacuation. Duodenal drainage usually shows hypochlorhydria and frequently a relative or absolute achlorhydria. No dark bile is obtained after the administration of magnesium sulfate, but is obtained after olive oil. Microscopic examination of the bile in characteristic instances shows large numbers of cholesterol crystals indicating a relatively increased concentration of cholesterol in the bile. Culture of the duodenal specimen of bile is negative when free hydrochloric acid is present in the gastric specimen.

When there is no free hydrochloric acid present, the duodenal culture will frequently show contamination by those organisms usually found in the nose and throat which have been swallowed and escaped the sterilizing action of the acid. In these instances a colon, typhoid or Welch bacillus is only taken to be supportive evidence of gall bladder infection.

The condition responds well to medical treatment. Olive oil should be given between meals to enhance the stimulation of the gall bladder

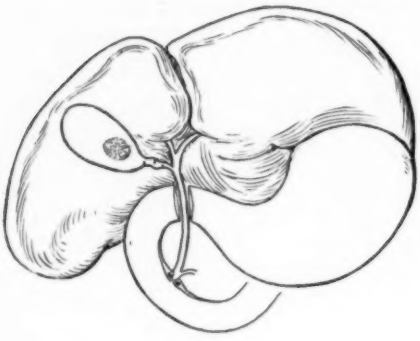


Fig. 35

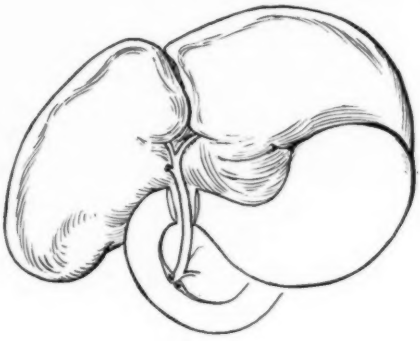


Fig. 36

and thus aid in its evacuation. All fats should not be eliminated from the diet since their effect upon the gall bladder wall is an essential part of the treatment. In patients with hypercholesterolemia, reduction of the cholesterol content of the diet is indicated. In those with hypochlorhydria or achlorhydria substitution therapy in the form of dilute hydrochloric acid with meals is a fixed routine. Correction of endocrine imbalances, such as hypothyroidism and obesity, is indicated as part of the general treatment.

Bile stasis is eventually followed by the sedimentation of cholesterol crystals and ultimately stone formation if these patients are not treated successfully (Fig. 35). The symptoms in this stage are similar to the pre-stone stage so long as the stone remains free in the gall bladder cavity. Roentgenography reveals a stone in a functioning gall bladder. The duodenal drainage is similar to the pre-stone stage. Surgery is now indicated to prevent the mechanical complication of impaction of a stone in the ampulla of the gall bladder. Cholecystectomy cures the patient of all his symptoms since it removes the initiating cause of the gall bladder dysfunction, its wall, as well as the result, the stone (Fig. 36). The prognosis is excellent so far as recurrence of symptoms is concerned in marked contrast to the hypertonic type. The cure of the initiating process which eventually leads to advanced pathology is effected by cholecystectomy before stone formation as well as after. Operation is not necessary in the primary stage, however, since specific medical treatment will relieve the patient and seems to prevent stone formation.

The type of stone found in hypotonic dyssynergia is of the choles-

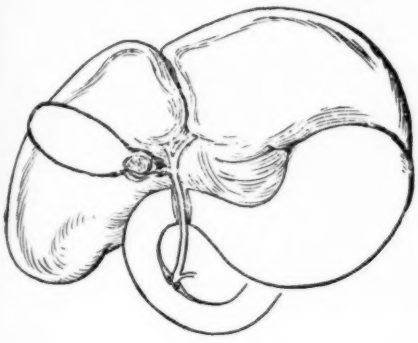


Fig. 37

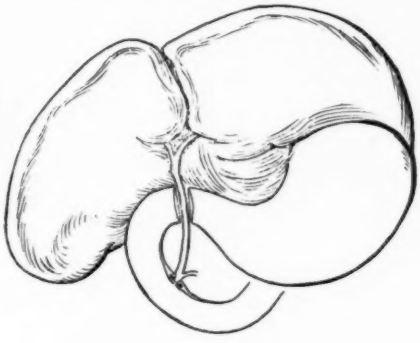


Fig. 38

terol variety and is most often single. Since no additional symptoms are due to the presence of the free stone in the cavity of the gall bladder, it is often discovered during roentgenographic examination for other lesions. If not discovered, it has a tendency after an indeterminate period of time to become impacted in the ampulla of the gall bladder (Fig. 37). Once in this situation, it may give rise to symptoms resembling the colicky attacks of hypertonic gall bladder but to a lesser degree. Colic of this type is characterized by not being relieved by amyl nitrite inhalation. After the initial crisis during which the stone becomes impacted in the ampulla, no colic may be experienced by the patient since the gall bladder wall tends to atonia. Discomfort in the right upper quadrant may be experienced especially following fat meals which stimulate gall bladder contractions. Roentgenographic examination of the individual in this stage of gall bladder disease shows no visualization of the gall bladder. Duodenal drainage reveals no concentrated bile even after stimulation with olive oil. Cultures are negative as a rule. Cholecystectomy at this time promptly and completely cures the patient's symptoms and terminates the course of the development of gall bladder disease in that individual (Fig. 38).

Should infection be superimposed on an obstructed gall bladder, there is the development of an empyema of the gall bladder (Fig. 39). Cholecystectomy will still cure the patient if performed early enough (Fig. 40). If the obstructed gall bladder is subjected to repeated low-grade attacks of inflammation, its wall becomes thickened, fibrotic and contracted. Small stones in the gall bladder are apt to be extruded into the common duct after engagement of the larger stone in

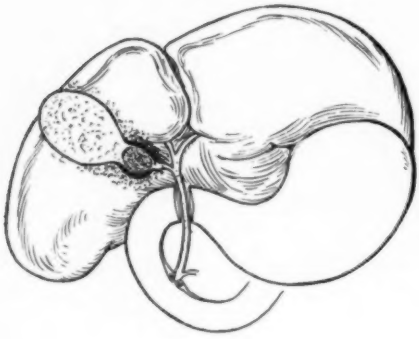


Fig. 39

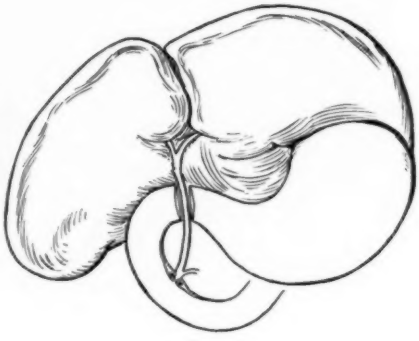


Fig. 40

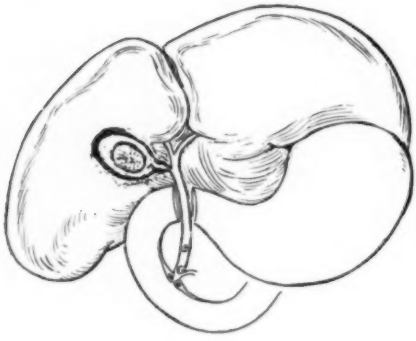


Fig. 41

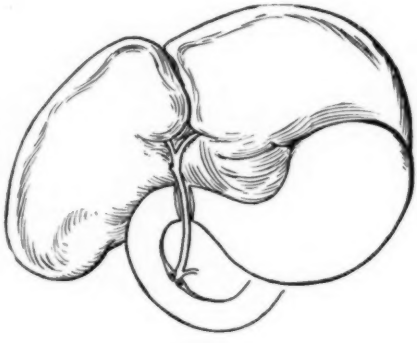


Fig. 42

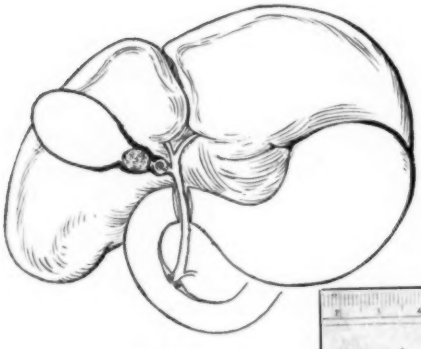


Fig. 43

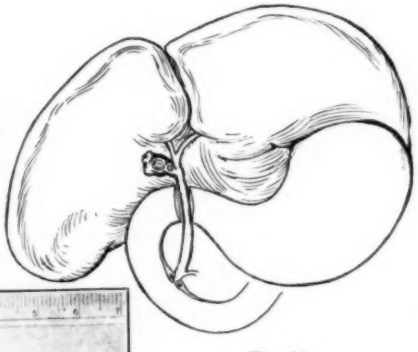


Fig. 44

Fig. 45 →

the entrance to the ampulla (Fig. 41). It is important when the cystic duct is found dilated to make sure at operation that the common duct is free from stones. Removal of the gall bladder and common duct stones at this stage cures the patient and terminates the progress of the disease in that individual (Fig. 42).

In cases where the obstructing stone in the ampulla is the only stone present in the gall bladder, the cystic duct which is proximal to the stone and in open communication with the common duct becomes dilated. Stasis occurs with sedimentation and possible formation of small calculi in the cystic duct (Fig. 43). At operation, the relatively small, dilated cystic duct with its contained calculi is sometimes overlooked and is left after the gall bladder has been removed (Fig. 44). The danger of such an overlooked remnant is the possibility of the small contained stones entering the common duct. Four such instances have been observed and operated upon at the New York Post-Graduate Hospital in the past two years. Figure 45 shows the remnant of cystic duct removed from a patient. For twenty years following an operation for the removal of the gall bladder the patient was perfectly well. He then had an acute attack of epigastric pain associated with chills, fever, and jaundice. At operation an ampulla and dilated cystic duct remnant were found. A small stone composed of cholesterol with an outer covering of calcium bilirubinate (Fig. 45) was found impacted at the lower end of the common duct, which in this instance, united with the pancreatic duct before entering the duodenum. The probability is that the stone was either overlooked at the first operation or formed in the portion of cystic duct that was left. For some reason which cannot be determined the stone, after a prolonged period of residence in the cystic duct, entered the common duct where it became impacted at the lower end. The inner portion of the stone resembled gall bladder stone formation; the outer common duct stone formation.

The majority of patients having hypotonic dyssynergia are operated upon during the secondary period of the disease in which the stone is free in the gall bladder or shortly after the onset of the third stage with impaction and obstruction of the cystic duct. Neglected cases or those refusing surgery will, of course, continue on to the later stages with possible permanent common duct involvement. Since the mortality and morbidity rate increases with each successive stage of gall bladder disease it is advantageous to both the patient and the physician to utilize surgery early in the course of the disease.

TABLE II

DISORDERS RESULTING IN DISTURBANCES IN THE CONCENTRATING FUNCTION OF THE GALL BLADDER

1. *Infectious cholecystitis*
2. *Reflux pancreatic juice*
3. *Abnormal concentration of special elements*
   (a) Bile Salts
   (b) Calcium–Calcified Gall Bladder Wall
   (c) Calcium Carbonate–"Milk of Calcium" Gall Bladder
   (d) Cholesterol–Cholesterosis

DISORDERS AFFECTING THE CONCENTRATING FUNCTION OF THE GALL BLADDER

Fifteen to twenty per cent of the patients coming to the Gall Bladder Clinic in the primary stage of gall bladder disease, show disorders resulting in disturbances in the concentrating function of the gall bladder as listed in Table II. The most common cause in this group is infectious inflammation. In recent years, however, non-bacterial causes of inflammation have been suggested as capable of affecting the mucosa and of interfering with its concentrating mechanism. One of these is the reflux of pancreatic juice into the gall bladder. A prerequisite for this is the union of the common and pancreatic ducts above the sphincter of Oddi. The exact way in which the pancreatic juice affects the gall bladder is not entirely clear. However, that it is capable of producing a chemical inflammation under proper conditions is not doubted.

Disturbances in concentration may also be in the direction of abnormal concentration or secretion of special elements of the bile with or without the associated loss in bile concentration as a whole. Examples are: One, excessive concentration of bile salts. This has been shown experimentally to be capable of producing very marked inflammatory changes in the gall bladder. Two, calcium concentration. The result is a calcified gall bladder wall. This is rare. Only three cases have been seen in the clinic in the past twelve years. Three, calcium carbonate secretion. This is the so-called "milk of calcium" gall bladder. The contents are semi-solid and resemble light gray putty with the other

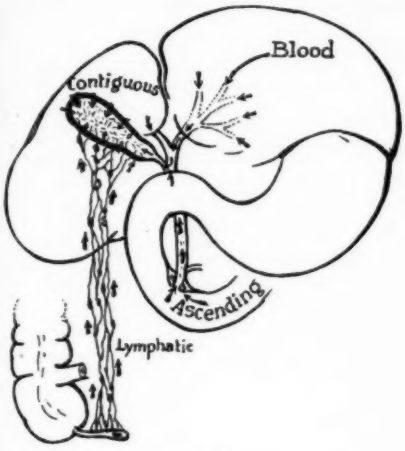


Fig. 46

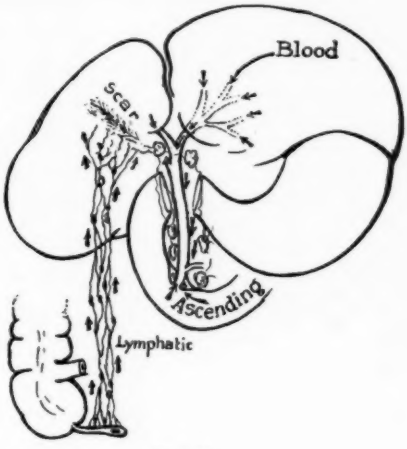


Fig. 47

elements of bile reduced or absent. The etiology is believed by some authorities to be associated in some way with obstruction of the cystic duct, infection of the gall bladder wall and secretion by the wall of the calcium carbonate. Those cases which have been seen at the New York Post-Graduate Hospital of this type were found to be sterile when removed and cultured. Four, cholesterol concentration. The controversy as to whether the gall bladder execretes or absorbs the cholesterol found in its wall has not been determined. The fact is that there is an abnormal concentration of cholesterol in the gall bladder mucosa in cholesterosis, commonly called "strawberry gall bladder."

INFECTIOUS CHOLECYSTITIS

About 10 per cent of all patients coming to the Gall Bladder Clinic in the pre-stone stage have a demonstrable infection as the primary initiating factor of gall bladder disease. The presence of any one of the other initiating factors of gall bladder disease such as a tortuous cystic duct, dyssynergia, etc. together with infection, arbitrarily classifies the patient in the group of disturbances in the filling and emptying mechanism rather than as one of primary infectious cholecystitis. The infection may have reached the gall bladder via the blood; may have ascended from the duodenum; may have spread via the lymphatics from some other intra-abdominal focus, e.g., duodenal ulcer (Fig. 46). While the history may

occasionally suggest the primary site of infection, it usually cannot be definitely determined at the time of examination. If the source is found, it is important to remove it. Removal of the gall bladder alone without the primary source will not always cure the patient of repeated attacks of infection and its effects on the biliary lymphatic zones (Fig. 47).

The special diagnostic signs of infectious cholecystitis are as follows:

1. Low-grade inflammatory pain of three to seven days duration.
2. Tenderness and rigidity in the right upper quadrant during an acute attack.
3. Sub-clinical jaundice (Icteric Index 7-10 units).
4. Faint or absent visualization of the gall bladder on roentgenography.
5. Crystalline sediment of calcium bilirubinate on duodenal drainage.
6. Positive culture of the specific organisms in the duodenal bile.

The organisms most commonly found in chronic infectious cholecystitis are B. typhosus, B. coli, B. Friedländer and rarely the streptococcus and staphylococcus groups. Cholecystectomy early in the course of the disease will result in the cure of the patient's symptoms and permanent interruption of the course of gall bladder disease when the site of the disturbance is contained within the gall bladder. Examination of the other intra-abdominal organs should be undertaken at operation, particularly the appendix as it is often the primary focus of infection. Structural deformities, sphincter of Oddi spasm, or gall bladder wall disturbances are not essential for infection to become residual in the gall bladder and cause a characteristic chronic infectious cholecystitis. The reason for infection becoming residual in the gall bladder is usually attributed to certain types of organisms being, or becoming, so resistant to concentrated bile that they are not affected by it. Such patients with chronic infection may not seek advice since the attacks of pain are of a low-grade nature and there may be long periods of freedom from symptoms. When a definite diagnosis of an existing chronic infectious cholecystitis is made, operation should not be unduly delayed as acute fulminating cholecystitis does occur in some patients prior to stone formation. The impression that this form of acute cholecystitis without stones is particularly dangerous probably springs from the serious type of organ-

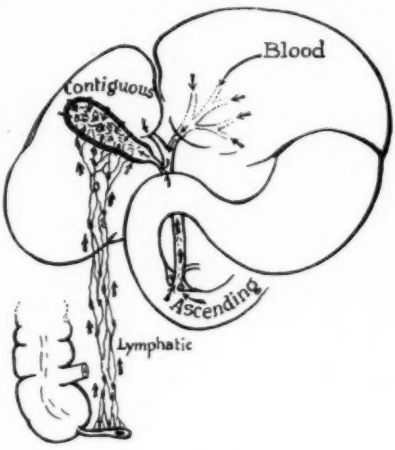


Fig. 48

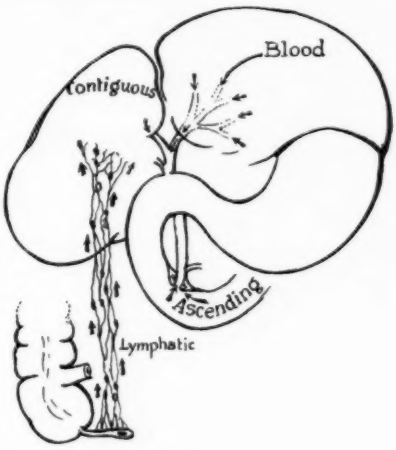


Fig. 49

isms that are capable of living and growing in a comparatively normal gall bladder.

In association with continued low-grade infection of the gall bladder, the composition of the bile is altered resulting in the precipitation of crystalline sediment, calcium bilirubinate, and the ultimate formation of small, irregular pigment stones "infectious stones" (Fig. 48). The clinical and laboratory findings in this stage are very similar to those found in the pre-stone stage. Surgery at this stage will still encompass and remove the condition as well as relieve symptoms and interrupt the course of development of the gall bladder disease process in the individual (Fig. 49). If, however, the patient does not seek advice, the next step is engagement and impaction of a stone in the cystic duct. Empyema of the gall bladder follows as there is infection already present (Fig. 50). At this stage there is severe pain with marked tenderness and rigidity in the right upper quadrant associated with fever, chills, and even sub-clinical jaundice. The patient appears fairly toxic and a palpable mass can be felt in the right upper quadrant. Roentgenography and duodenal drainage usually are not advisable at this time and are not deemed necessary as has been already pointed out. The clinical picture as outlined above is sufficient for an abdominal exploratory operation when a characteristic mass is present in the right upper quadrant.

The operation should be performed during the acute stage of infection, preferably between the second and fourth days. An analysis of the

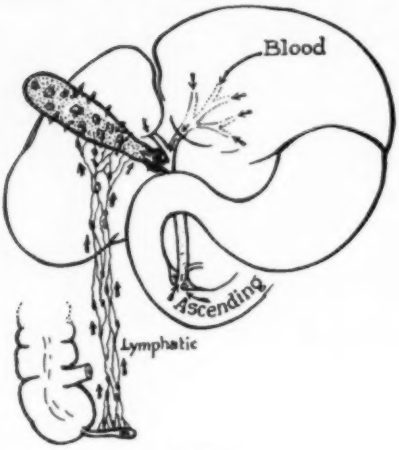


Fig. 50

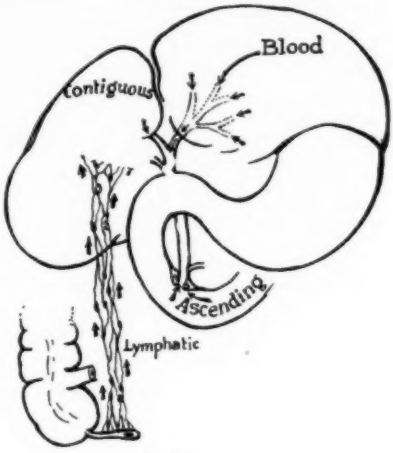


Fig. 51

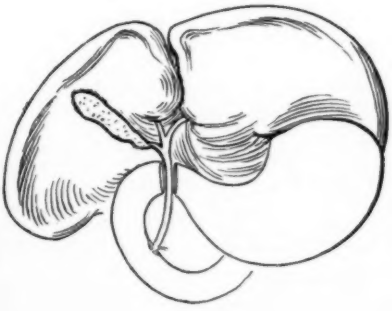


Fig. 53

Fig. 52

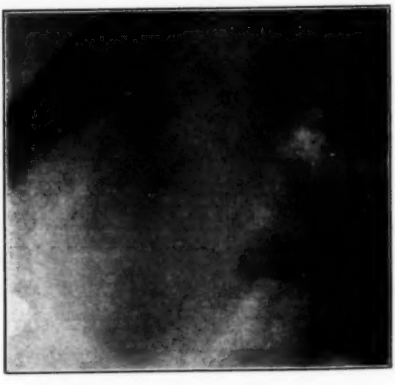
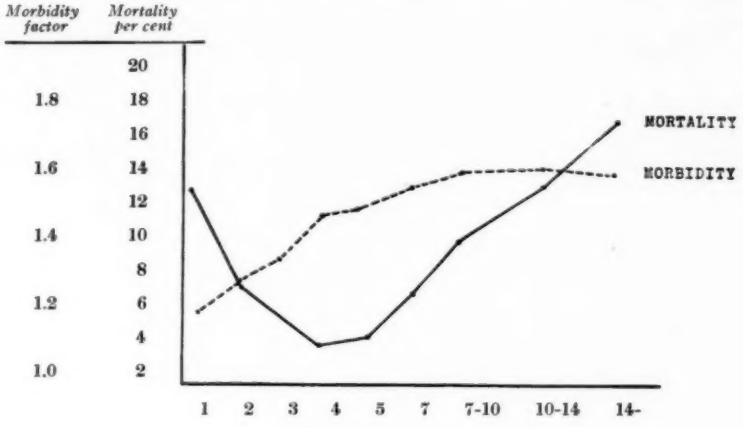


Fig. 54

TABLE III

THE MORBIDITY AND MORTALITY IN SURGERY ON ACUTE CHOLECYSTITIS IN RELATION TO THE DURATION OF THE PRESENT ILLNESS



data on 500 patients with acute infectious cholecystitis at the New York Post-Graduate Hospital is shown in Table III. Mortality and morbidity are seen to increase after the fourth day of illness. The actual operative procedure to be followed will be determined largely by the condition of the patient. Under favorable circumstances, a cholecystectomy is done with the resultant cure of the patient (Fig. 51). Under unfavorable circumstances, however, one may be compelled merely to do a cholecystostomy (Fig. 52). It should be emphasized, however, that a cholecystostomy, in contrast to a cholecystectomy, is not a curative procedure. The infection remains in the gall bladder after removal of the cholecystostomy tube (Fig. 53). Such a gall bladder when followed by studies of its function by duodenal drainage, cultures and roengenogram examination over a period of many years never seems to regain its normal function nor rid itself of the B. typhosus or B. coli. Roentgenography following a cholecystostomy continues to show either faint visualization (Fig. 54) or no visualization of the gall bladder. Positive specimens of duodenal cultural examinations persist. Recurrence of the clinical picture with low-grade jaundice is the rule, and an indication that removal of the gall bladder as well as the stone is necessary for a cure in these cases. Recognition of this fact together with the good

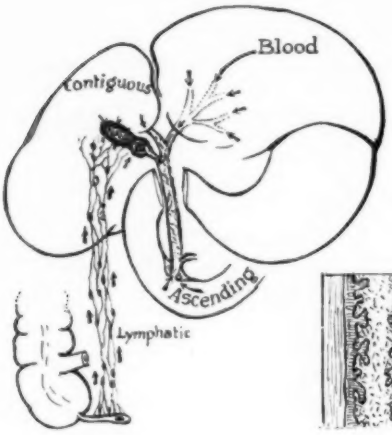


Fig. 55

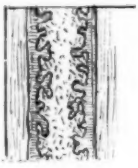


Fig. 55A

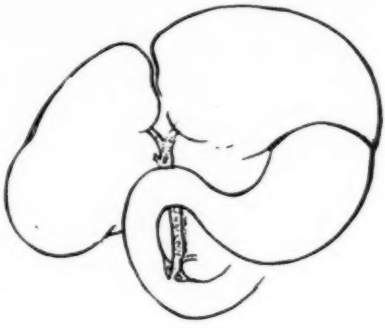


Fig. 56

results obtained by cholecystectomy probably led clinicians to the belief that the majority of disease processes in the gall bladder were on the basis of an initial infection.

Gall bladders which have been subjected to repeated episodes of empyema become contracted and fibrotic (Fig. 55). The infection extends into the common duct and after a period of time becomes firmly entrenched in the sacculi (Fig. 55A). After this has occurred, simple cholecystectomy will remove the primary site of the infection but does not cure the condition. It does not prevent the progress of the disease since the infection now has extended to, and permanently involved the common duct (Fig. 56). Medical and surgical attempts to eradicate chronic, residual infection in the common duct, especially that due to B. coli and B. Friedländer, have yielded poor results. Concentrations of sulfanilamide in the bile up to 15 mgm. per cent have failed to eradicate the B. coli and B. Friedländer. Similar disappointing results were obtained after the use of sulfathiazole, sulfapyridine, sulfaguanadine, phenolmercuric nitrite, vaccines and a host of so-called biliary antiseptics.

It is of the utmost importance, for two reasons, to insure a free flow of bile from a common duct in which chronic infection has become entrenched. First, stasis will result in stone formation and, secondly, acute pancreatitis in cases where the common duct and pancreatic duct unite must be expected following the impaction of the stone at the

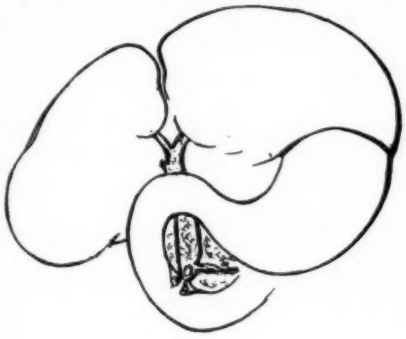


Fig. 57

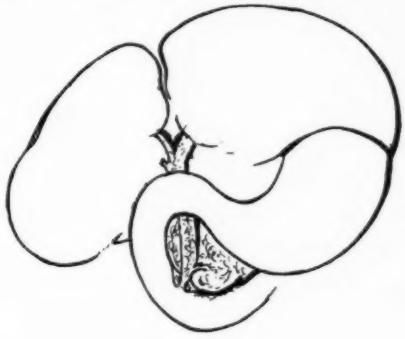


Fig. 58

ampulla with regurgitation of infected bile into the pancreas (Fig. 57). Removal of the common duct stone (Fig. 58) must also be followed by medical treatment or else the probability is that the patient will reform another stone. So long as a free flow of bile is assured, the latent infection may be expected to remain quiescent and cause little if any actual symptoms or disability.

Summary: Formerly infectious inflammation was considered the sole cause of interference with the concentrating mechanism of the gall bladder. However, it is now realized that other factors beside infection may produce inflammatory changes. Infectious cholecystitis as an initiating factor constitutes about 10 per cent of primary gall bladder disease. The infection is at first localized in the gall bladder and may be permanently eradicated by cholecystectomy prior to extension to, and involvement of, the wall of the common duct. In the later stages the infection will permanently involve the common duct. At this time removal of the primary site, i.e., the gall bladder, does not influence the infection in the common duct. Attempts to eradicate the infection from a chronically involved common duct have until now been unsuccessful. Treatment is directed toward maintaining a free flow of bile to prevent stasis.

Failure of medical means, as indicated by repeated occurrence of attacks of pain, fever, chills and jaundice associated with signs of liver damage from recurrent stone formation with obstruction (Fig. 33) are all indications for surgical interference. 'By-pass' operations providing a permanent drainage outlet between the common duct and duodenum are useful in this and other types of chronic biliary obstruction (Fig. 32C).

REFLUX OF PANCREATIC JUICE

The possibility of a reflux of pancreatic ferments causing inflammatory changes in the gall bladder wall resembling those of bacterial inflammation has received much attention in recent years. It is significant that the pancreatic duct unites with the common duct above the sphincter of Oddi in the majority of people (various authorities quote from 45 to 84 per cent). Any obstruction, organic or functional, at the ampulla of Vater predisposes to the reflux of pancreatic ferments into the gall bladder. It probably occurs during periods of fasting even without the presence of obstruction. An analysis of the bile in 200 gall bladders removed at the New York Post-Graduate Hospital has confirmed the reflux of pancreatice juices in the majority of people. One or more of the pancreatic ferments were present in 59 per cent of the noncalculous gall bladders, in 74 per cent of gall bladders with stones and in the contents of 63 per cent of obstructed gall bladders. The presence or absence of pancreatic ferments in the gall bladder bile could not be shown by a study of the data to have any consistent effect upon the gall bladder wall or the formation of stones. The finding of pancreatic ferments in the gall bladder is of academic interest so far. Further study is necessary to determine just what importance such a reflux of ferments may have upon the development of pathology in that organ. On the other hand, there is little room for doubting the importance of this anatomical relationship in the development of acute pancreatitis.

The normal flow of bile in the fasting state is directed from the liver and bile ducts into the gall bladder where it is concentrated, a mechanism comparable to the flow of bile through the gall bladder in patients having a cholecystostomy. This process is conducive to a flow of pancreatic juice into the common duct and upward, following the general current, into the gall bladder. Obstruction of the gall bladder by stone, or its surgical removal, diverts the bile current between meals from the gall bladder to a continuous flow into the duodenum. Pathological pressure developed in the common duct by increased resistance to the flow of bile through the sphincter of Oddi permits the reflux of bile into the pancreas and the production of pancreatitis. The inflammatory reaction is greatly enhanced by the presence of bacteria. After the third stage of gall bladder disease has been reached, i.e., obstructed cystic duct and gall bladder obliteration, infection is usually present whatever the initiating cause of the disease. The anatomic relationship described, therefore, is of importance in the subsequent course of events.

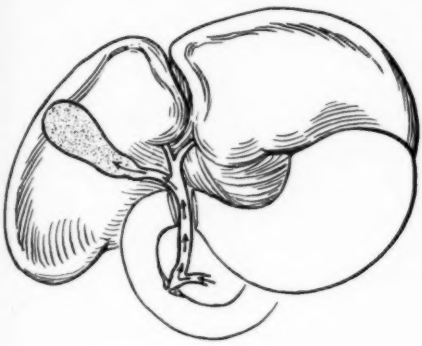


Fig. 59

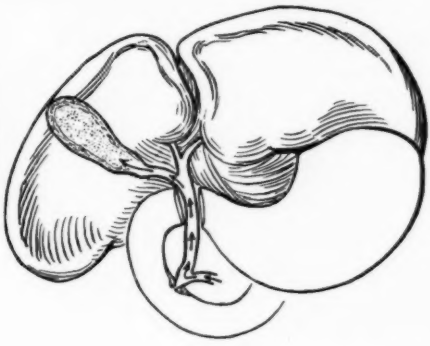


Fig. 60

PRE-STONE STAGE

MECHANISM

Cause

Reflux of pancreatic ferments into gall bladder. (Fig. 59.)

Effect

Questionable. Possible chemical cholecystitis. (Fig. 60.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure.

SPECIAL DIAGNOSTIC POINTS

No pre-operative means of determining anatomical relationship of pancreatic and common ducts.

History

No characteristic symptoms of the existence of pancreatic ferments in the gall bladder at any stage of gall bladder disease.

Physical Signs

Not distinctive.

Roentgenogram

Not distinctive.

Duodenal Drainage

Not distinctive. Culture of duodenal specimen of bile sterile in all patients examined.

REFLUX OF PANCREATIC JUICE *(continued)*

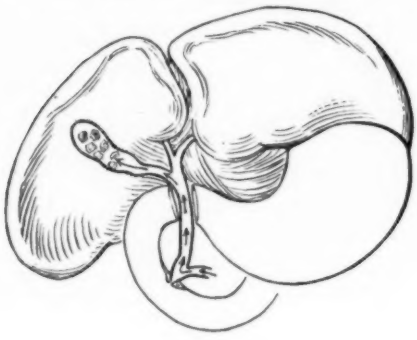


Fig. 61

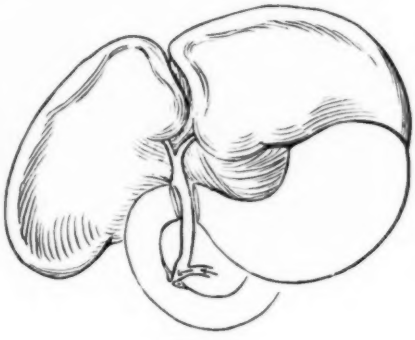


Fig. 62

STONE STAGE

MECHANISM

Effect

Questionable. Altered relations of constituents of bile. Precipitation of crystals. Formation of stones rich in calcium bilirubinate. (Fig. 61.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure. (Fig. 62.)

SPECIAL DIAGNOSTIC POINTS

History

Not distinctive.

Physical Signs

Not distinctive.

Roentgenogram

Not distinctive.

Duodenal Drainage

Not distinctive. Culture of duodenal specimen of bile sterile in all patients examined.

Summary: While the effect of pancreatic ferments on the gall bladder wall may be open to question, the union of the common and pancreatic ducts above the sphincter of Oddi is of great importance since reflux of infected bile into the pancreas may produce acute pancreatitis (Fig. 63). Pre-operatively the anatomical relationship of the two ducts cannot be determined. Postoperatively, however, in cases with tubes in the gall bladder or common duct, introduction of a contrast substance (hippuran, diotrast, lipiodol) often shows the union of the ducts (Fig. 64).

Reflux of bile into the pancreas is the result of pathological pressure in the common duct; the result of obstruction at its lower end. Com-

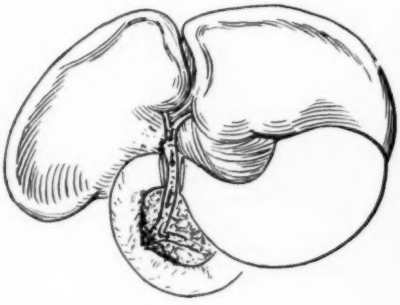


Fig. 63

Fig. 64

Fig. 65 Fig. 66 Fig. 67

mon causes of this obstruction are impacted stone, spasm, or edema of the sphincter. Of the three, common duct stone is the most common. Figure 65 shows a stone in the lower end of the common duct in a patient in whom the anatomical arrangement of the ducts predisposed to pancreatitis. A cholangiogram done postoperatively (Fig. 66) reveals the stone removed. Such a patient requires careful postoperative medical management to prevent sphincter spasm and further reflux of bile into the pancreas. This is especially important if the bile is infected. In contrast, Figure 67 shows common duct stones in a patient in whom the common and pancreatic ducts do not unite above the sphincter of Oddi. Reflux of bile into the pancreas is not a danger in such a patient.

ABNORMAL CONCENTRATION SPECIAL ELEMENTS

a. *Bile Salts*

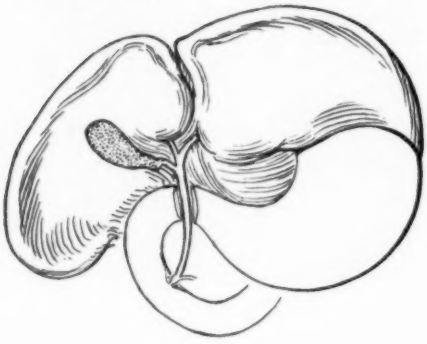


Fig. 68

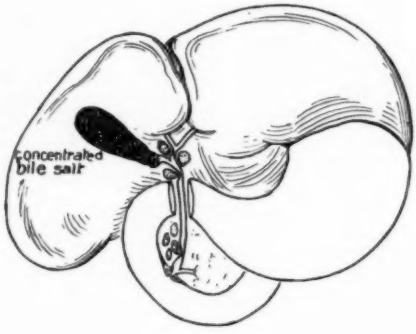


Fig. 69

MECHANISM

Cause

Excessive concentration of bile salts. Exact mode of action not definitely known. (Fig. 68.)

Effect

Inflammation of gall bladder. Gangrene of gall bladder wall. Very little inflammatory reaction preceding gangrene. (Fig. 69.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Uncertain.

SPECIAL DIAGNOSTIC POINTS

Etiology not determinable preoperatively.

History

Same as any other acute inflammatory cholecystitis.

Physical Signs

Jaundice without anemia. Rigidity in right upper quadrant. Excessive rise in temperature.

Roentgenogram

Faint or no visualization of the gall bladder. Roentgenography rarely done in presence of marked acute symptoms.

Duodenal Drainage

Not diagnostic.

Summary: The finding of acute inflammation in gall bladders containing dark sterile bile during the first two days of an acute attack have suggested a chemical basis for the inflammation. Marked excessive concentration of bile salts results in early, dry gangrene. The entire gall bladder wall may be found to have the lifeless appearance of tissue sud-

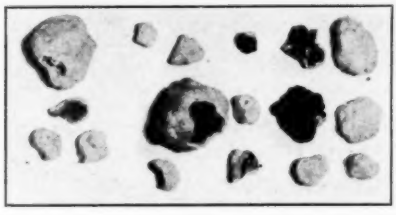
denly deprived of its blood supply. Operation in such instances after the fourth day of illness reveals abscess formation at the site of the gall bladder with positive cultures. This finding has led to the suggestion that the primary cause is chemical followed by the superimposition of infection. Less marked concentration under similar circumstances will occasionally reveal an acutely inflamed gall bladder with enlarged lymph nodes at the cystic duct and along the common duct.

b. *Calcium—Calcified Gall Bladder Wall*

Fig. 70

Fig. 71

Fig. 72 →



MECHANISM

Cause

Not definitely known.

Effect

1. Deposition of calcium in wall of gall bladder. (Fig. 70.)
2. Formation of calcium carbonate stones. (Fig. 72.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure.

SPECIAL DIAGNOSTIC POINTS

History—No definite symptoms unless stone becomes impacted.

Physical Signs

Frequently associated with low-grade jaundice.

Roentgenogram (Fig. 71)

Irregular calcification of gall bladder wall.

Duodenal Drainage

Irregular response—not diagnostic. Culture of duodenal specimen of bile sterile in all patients examined.

c. *Calcium Carbonate—"Milk of Calcium" Gall Bladder*

Fig. 73

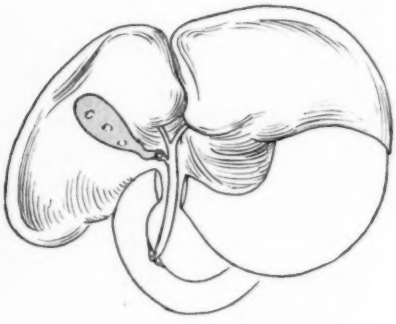


Fig. 74

MECHANISM

Cause

Not definitely known. Believed associated with inflammation and obstruction of cystic duct.

Effect

(a) Abnormal appearance of calcium in gall bladder cavity.
(b) Calcium carbonate deposited "milk of calcium." Resembles putty.
(c) Calcium carbonate stones formed.

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure.

SPECIAL DIAGNOSTIC POINTS

History

Right upper quadrant or epigastric distress with excessive gas.

Physical Signs

Associated with low-grade jaundice in patients seen in this clinic.

Roentgenogram

(a) Outline of gall bladder after dye given frequently mistaken for normal visualization.
(b) Lack of alteration in gall bladder shadow after fatty meal often mistaken for retention of dye in gall bladder.
(c) Roentgenography without dye – gall bladder visible. (Fig. 73.)
(d) Stone may be seen in cystic duct although gall bladder well visualized. (Fig. 74.)

Duodenal Drainage

Not diagnostic. Culture of duodenal specimen of bile sterile in all patients examined.

d. *Cholesterol–"Cholesterosis"*

Fig. 75*

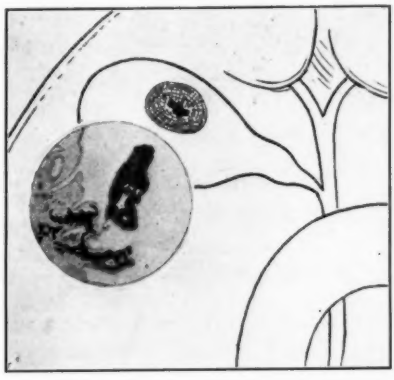


Fig. 76

MECHANISM

Cause

Unknown.

Effect

(a) Deposition of cholesterol in mucous membrane of gall bladder (Fig. 75.)

(b) Possible detachment of papilloma which forms center for stone formation. (Fig. 76.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure.

SPECIAL DIAGNOSTIC POINTS

History

Not distinctive–see summary.

Physical Signs

Negative.

Roentgenogram

Normal visualization. Rapid emptying of gall bladder after fatty meal suggestive but not conclusive.

Duodenal Drainage

Not significant. Culture of duodenal specimen of bile sterile in all patients examined.

Summary: An examination of the data in patients found at operation to have cholesterosis does not reveal symptoms suggesting the presence of this condition. It is frequently found associated with all stages of gall bladder disease; even in the common duct wall in advanced choledochitis. As a rule, its presence is not suspected and looked for pre-operatively. At present it does not play an important part in the concept of gall bladder disease. It may possibly be found to be of greater importance as our knowledge of cause and effect increases.

* Reproduced with permission from Boyd's Surgical Pathology, W. B. Saunders & Co., Philadelphia.

TABLE IV

DISORDERS IN BLOOD AND METABOLISM RESULTING IN DISTURBANCES OF THE GALL BLADDER

1. *Hemolytic Jaundice*
   Congenital hemolytic icterus, "sickle cell" anemia, etc.
2. *Cholesterol Metabolism*
   (a) Pregnancy
   (b) Obesity

DISORDERS IN BLOOD AND METABOLISM AFFECTING THE GALL BLADDER

The last etiological group to be considered includes those general disorders which manifest themselves in disturbance of gall bladder function (Table IV). Included is hemolytic jaundice, a blood dyscrasia in which there is an increased fragility of red blood cells, e.g., congenital hemolytic icterus, "sickle cell" anemia, etc. The excessive breakdown of red cells leads to an increased concentration of calcium bilirubinate in the bile with subsequent precipitation and stone formation. Pigment stones have been found in the gall bladder and biliary tract in 60 per cent of cases with congenital hemolytic icterus.

In pregnancy and obesity the basic disorder is an upset in the cholesterol metabolism.

Strictly speaking the initial upset in this group is in the concentration of special elements in the bile. In contrast to the abnormal concentration of special bile elements listed in Table II, however, the initiating mechanism lies *outside* the biliary tract. The condition is not limited solely to the biliary tract, but merely expresses itself there in one form. Thus, the calcium bilirubinate stones in hemolytic jaundice, and the cholesterol stones in pregnancy and obesity are usually found in an otherwise normally functioning gall bladder. Once stones have formed, however, the superadded progressive complications already described (impaction of stone in cystic duct, etc.) may occur.

HEMOLYTIC JAUNDICE

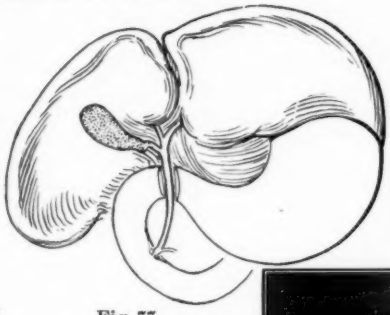


Fig. 77

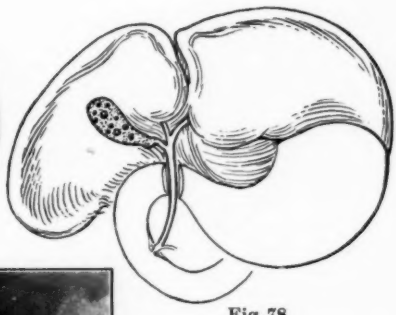
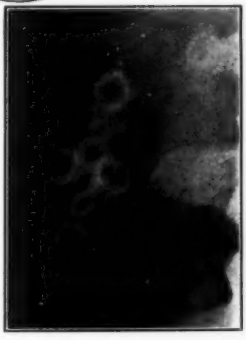


Fig. 78

Fig. 79 →



MECHANISM

Cause

Hemolysis of red blood cells.

Effect

1. Excessive amount of calcium bilirubinate in bile. (Fig. 77.)
2. Precipitation of pigment and stone formation. (Fig. 78.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Uncertain. May form common duct stones.

SPECIAL DIAGNOSTIC POINTS

History

No symptoms referrable to gall bladder. Hemolytic jaundice, anemia, etc.

Physical Signs

Jaundice, anemia, increased red blood cell fragility with spherocytosis, "sickling," etc. Positive indirect Van den Bergh reaction.

Roentgenogram

Normally functioning gall bladder. If stones present, well visualized. (Fig. 79.)

Duodenal Drainage

Normal response. Crystalline sediment—calcium bilirubinate.

Culture of duodenal specimen of bile sterile in all patients examined.

Fig. 80

Fig. 81

CHOLESTEROL METABOLISM

a. *Pregnancy*

The association of pregnancy and gall stones is well known. Experimentally, the gall bladder in pregnant pigs has been shown to be less responsive to the stimulating action of cholecystokinin than in the non-pregnant. Furthermore, the blood and bile in pregnant women has a higher concentration of cholesterol than normal. These two factors, stasis and a relative preponderance of cholesterol in the bile, predispose to the precipitation of crystals and the formation of stones. This mechanism may occur in any type of gall bladder. Figure 80 shows the gall bladder of a patient seen at the clinic complaining of distress in the right upper quadrant. Figure 81 shows the gall bladder of the same patient seen after a pregnancy had occurred. Many negative shadows, all of the same size, can be seen. The probability is that the intervening pregnancy with its stasis and upset in cholesterol metabolism was responsible for the stone formation.

b. *Obesity*

Here again the basic disorder as regards the gall bladder is an upset in the cholesterol metabolism. The exact association between obesity and gall bladder disorder is not known. Most obese individuals, however, with associated gall bladder disturbance tend toward hypotonic dyssynergia.

THE DIAGNOSIS AND PROGNOSIS OF BRAIN TUMORS*

GILBERT HORRAX†

IN considering the diagnosis of brain tumor, two features must be kept in mind constantly. First, has the patient a brain tumor or some other type of intracranial lesion which simulates tumor, and second, if a tumor is present, what is its situation and its pathology? With our present neurologic knowledge and diagnostic methods, the first of these questions can be answered in practically every case provided the patient or his responsible relatives consent to thorough diagnostic measures. With regard to the second question, we are likewise usually able to locate the tumor exactly, but its pathology, predictable in a large and ever increasing percentage of cases, often cannot be determined prior to operation.

DIAGNOSIS

From the standpoint of diagnosis, there are roughly two clinical types of brain tumor: first, that which presents the well-known symptoms and signs of brain tumor, and secondly, that which presents many different neurologic or other findings but lacks the usual textbook picture.

With regard to the first type, when the complaints include headaches and vomiting and the ophthalmoscope shows choking of the optic disks, the burden of proof is obviously on the person who says that the diagnosis is not brain tumor. Nevertheless, there are certain other conditions which may produce this time-honored triad, and from which tumor must be differentiated. Among these are brain abscess, which may be suspected from a preceding infectious process, particularly an old otitis media, chronic mastoiditis, frontal sinusitis, scalp infection or bronchiectasis, to mention a few of the common possibilities. Another con-

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dition which is recognized as a clinical entity is the so-called "increased intracranial pressure without tumor," that is pseudotumor or arachnoiditis, which may be surmised when pressure symptoms, together with choked disks are acute, and the neurologic signs absolutely lacking. Often this little understood, possibly inflammatory disturbance seems to be almost epidemic in character. The diagnosis can be made with certainty only by a ventriculogram which shows normal-sized ventricles in normal position. Malignant hypertension may also cause headaches and choked disks. As a rule, the diagnosis can be made on the basis of the blood pressure findings, together with evidence of cardiorenal disease, but when the systolic and diastolic pressures are only moderately elevated, an air study may be indicated to be perfectly sure that a growth is not overlooked. A chronic subdural hematoma may simulate tumor almost exactly, but the bilateral trephine holes used in carrying out the ordinary ventriculogram and situated over each parieto-occipital region, will almost inevitably disclose a unilateral or bilateral hematoma and thus confirm the diagnosis before the air study is done. Meningovascular lues and tuberculous meningitis should also be mentioned as conditions sometimes mistaken for brain tumor, but as a rule there is little difficulty in differentiating them by means of spinal fluid studies.

I feel obliged to extend a word of caution in using lumbar puncture as a diagnostic measure in probable brain tumor. It is seldom necessary in making such a diagnosis and, except in rare instances, adds nothing which cannot be learned more safely by means of careful neurologic study together with a ventriculogram when indicated. In trained hands and with due caution, accidents are rare, but the danger is not purely theoretical, avoidable deaths having occurred in practically all large neurologic and neurosurgical clinics where this measure is undertaken routinely.

Under the second category of patients, that is, those who do not have choked disks and other usual manifestations of brain tumor, a variety of neurologic, ophthalmologic and otologic evidences may have led to the suspicion of tumor, and for this reason, the patients must be studied with such a lesion in mind. Among these symptoms I would mention particularly focal or generalized convulsions, slow visual failure with some degree of unexplained optic atrophy, changes of personality in the absence of cerebral arteriosclerosis or evidence of some clear-cut recognizable psychosis, increasing unilateral deafness, staggering, or a

slowly progressive hemiparesis which at first was thought to be due to cerebral thrombosis.

In patients with these symptoms and signs, the diagnosis may be difficult and entail elaborate study. A careful, chronologic history together with a neurologic examination are the first requisites, but in addition, roentgenologic examinations of the skull, visual field examinations with small test objects, caloric tests, electro-encephalogram, and either an air encephalogram or ventriculogram may all be necessary. At times a careful lumbar puncture may give useful information.

As a rule, the differential possibilities are such conditions as cerebrovascular disease, multiple sclerosis, labyrinthitis, posttraumatic headache and dizziness, platybasia, and occasionally, primary anemia or psychoses of various sorts.

Situation and Pathology

With regard to the situation and pathology of brain tumor, it is well known that the brain harbors a large variety of tumors, but what is not so well known is the fact that the life histories and the clinical syndromes characteristic of certain types of growths in certain situations have been worked out in elaborate detail in the course of the last twenty-five years. The late Harvey Cushing and his associates were responsible for much of this information.

For the purposes of our present study, we may divide brain tumors into two groups so far as the diagnosis of their situation and pathology is concerned. In the first group are those tumors which as a rule can be recognized with a high degree of accuracy from the symptoms and objective neurologic or other clinical signs, which they produce and in the second, those which give no characteristic evidence of their whereabouts.

In a general way, but by no means without exception, the first group includes largely those tumors which are benign, encapsulated and favorable for complete enucleation, that is, certain of the meningiomas, the acoustic neuromas, the pituitary adenomas and some benign but uncommon tumors such as cholesteatomas or slowly growing gliomas which give characteristic roentgenologic findings. Also in this category are the somewhat less favorable tumors such as the congenital cysts of Rathke's pouch, pinealomas and some aneurysms which should be classed as tumors. In this short discussion only the briefest possible men-

tion can be made of the diagnostic features of these tumors.

1. Meningiomas are the well-known, firm, encapsulated growths which are attached to the dura and occur in various favorite situations. Those under the frontal lobes give slow mental changes, loss of the olfactory sense, and often optic nerve atrophy on one side and papilledema on the other, the syndrome of Foster Kennedy. The small meningiomas situated just above the sella turcica cause gradual failure of vision, optic nerve atrophy and bitemporal defects of the visual fields. They are differentiated from pituitary adenomas because the sella is not enlarged and pituitary functions are not lost. Meningiomas arising from the greater wing of the sphenoid often cause great hypertrophy of the bone in this area by tumor cells infiltrating the bone, and the eye on the affected side is pushed forward to a considerable degree (unilateral exophthalmos). Other meningiomas at various places over the cerebral convexities frequently cause characteristic bony enostoses and an increase in vascularity of the skull which is shown by the roentgenogram.

2. The syndrome of acoustic tumors, which are the common cerebellopontile angle growths, is now well known. A careful, chronologic history usually starts with unilateral tinnitus followed by increasing deafness in that ear, and then numbness on the same side of the face, staggering, headache, and finally, failing vision, dysarthria and dysphasia if the tumor is not recognized and removed. Objectively there is slow nystagmus, ataxia and an absent caloric response from the affected ear. The optic disks may show choking.

3. Adenomas of the pituitary gland present little diagnostic difficulty. The familiar triad of optic atrophy, bitemporal hemianopsia and a greatly enlarged sella turcica, as shown in the roentgenogram, can hardly be mistaken, especially when there are the usual evidences of pituitary dysfunction, such as amenorrhea in the female, loss of libido and feminine distribution of body hair in the male, a lowered basal metabolic rate, and increased carbohydrate tolerance. Occasionally an aneurysm in this situation may give signs which are extremely similar.

4. Of the more unusual tumors whose site and character often may be recognized by the roentgenogram, diploetic cholesteatomas show a scalloped outline of bony excavation. Craniopharyngiomas or Rathke's pouch cysts cause deformation of the sella often with calcification above it, and either choked disks or optic atrophy according to whether they protrude posteriorly or anteriorly to the chiasm. Certain calcified gli-

omas, notably the oligodendrogliomas, are likely to have a characteristic roentgenogram, and the same is true of some intracranial aneurysms. Pinealomas are rather rare tumors, but may be recognized with fair accuracy from the neurologic features of pupillary inactivity to light and loss of conjugate movements of the eyeballs upward above the horizontal plane. They also give a characteristic ventriculographic picture which shows the tumor shadow in the posterior portion of the third ventricle.

The tumors in the second group seldom or never give any neurologic or other evidence of their situation, hence this must be determined by means of air ventriculography. This group includes many of the large, infiltrating gliomas of all kinds occupying the so-called silent areas of the brain. Indeed the diagnosis of a considerable number of cerebellar tumors, both benign and malignant, can be made with certainty only by resorting to air studies, since cerebellar symptomatology may be inconclusive. In addition to the gliomas both above and below the tentorium, meningiomas which do not show roentgenologic changes or a characteristic clinical syndrome will likewise require air studies. Other tumors in this second group are those in the region of the third ventricle, a good many of the metastatic growths, and certain of the more rare lesions which need no enumeration.

Prognosis

Needless to say, the outlook for permanent useful life in a patient harboring a brain tumor is dependent upon complete removal of the tumor without damage to important neighboring structures. Recurrence is inevitable unless the growth is entirely removed. Although some tumors grow very slowly and partial removal may give several years of freedom from symptoms, nevertheless our aim should be total extirpation of all benign growths except in extremely rare circumstances. Fortunately with modern equipment including electrosurgery and a well organized neurosurgical team, this is now possible in a high percentage of cases. Even in the infiltrating tumors, if a radical, subtotal extirpation is done, and I believe it should be, many patients will have surprisingly long periods of normal and useful life, occasionally five or even ten years if a slowly growing glioma is encountered.

The use of roentgen therapy for malignant brain tumors, with the exception of medulloblastomas, pinealomas and occasionally oligoden-

drogliomas has been completely disappointing, in my experience, and any favorable results after such roentgen therapy could just as well have been due either to the tumor removal or to the decompression which may have been left at the time of operation. Roentgen therapy deserves a trial in cases of early pituitary adenoma since a certain number of these tumors are radiosensitive, but it is tragic to see, not infrequently, patients who have become blind because this treatment was persisted in until the optic nerves became completely atrophied when an earlier operation might have restored nearly normal vision.

Concerning prognosis we can now be infinitely more specific than in the earlier years of neurosurgery when all brain tumors were regarded as relatively hopeless lesions, and the occasional long survival of a patient from whom a tumor had been removed was regarded as an interesting and rare surgical curiosity. The largest and most exhaustively studied series of verified brain tumors is that of Cushing,[1] and in 1935 Eisenhardt[2] reported the end results of these patients, listing those who had survived five years or longer. There were 2,000 cases in the series, and of these about 1,500 survived the operation and the subsequent period of hospitalization. Of this number, almost one third or 33 1/3 per cent had lived from five to twenty-eight years up to seven years ago. Obviously, many more would now be included in this survival list if the figures were brought up to date.

These statistics did not include a discussion of useful life, but at least they are most enlightening from the standpoint of actual survival, especially since this series dates from the very beginning of neurosurgery in this country. If only the last ten or fifteen years had been reviewed, the results would unquestionably have been even more striking. Also, the series considers all tumors, benign and malignant, but obviously the patients who survived longest are those who harbored growths favorable for complete removal.

In an attempt to obtain information about useful survival of patients with brain tumor, that is, those who after operation either went back to their original occupation or to some useful type of work, I reviewed my own series of 400 verified tumors from November, 1932, to June, 1939. This therefore gives a follow-up period of from three and a half to eight years. It was apparent, as would be expected, that those who had done best were in the group of benign or favorable tumors, that is, those from whom the tumor could or should have been completely removed.

and it was on this group only that I made my study.[3] Well over one-half of all my patients fell into this favorable category, and although the tumors of many others were radically but subtotally extirpated and the patients had useful survival periods, they were not included in this group.

The favorable tumors consisted mostly of meningiomas, acoustic neuromas, pituitary adenomas, gliomatous and hemangiomatous cysts of the cerebellum, and a rather large group of uncommon tumors, the names of which are not pertinent here. All told, this favorable group comprised 218* of the 400 tumors, or 54.5 per cent. The operative mortality was 12.3 per cent (27 patients), and 16 other patients had died at various times subsequently. Of the survivors, 27 have severe disabilities which prevent them from engaging in useful occupations, leaving 148 patients or 67.8 per cent of the original 218 who are living and actively engaged in some form of work. If one takes the percentage only of the 191 who survived the operation, the figure of useful life rises to 77.6 per cent.

In general terms, therefore, somewhat over half of all brain tumors are favorable for complete extirpation, and of those patients who survive operation about three-fourths ought to be returned to useful life. As stated before, this figure does not include a fair number of patients who have tumors which cannot be completely eradicated and yet who may have several years of useful existence after their tumors have been radically but subtotally removed.

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* This and subsequent figures are slightly different from those in the article quoted due to changes in later follow-up records.

SOME RECENT ADVANCES IN THERAPEUTICS, INCLUDING THE NEWER DRUGS OF THE SULFONAMIDE GROUP*

HARRY GOLD

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Bio-chemotherapeutic Agents. During the period of intense growth of the sulfonamide problem, another and quite unrelated field of chemotherapy was subjected to active cultivation. The present products of this development are represented by the names tyrothricin, tyrocidine, gramicidin and penicillin.

The source of these antibacterial agents is the living cell. It has long been known that the living cell is a storehouse of specific catalysts capable of performing almost every type of biochemical reaction.[1] This fact has been utilized in a large variety of scientific and practical problems. It is involved in the phenomenon of "antibiosis," long known to bacteriologists and biologists as the unfavorable effect of the life process of one species of cell on those of another existing in the same environment. This phenomenon was brought close to the side of therapeutics by the basic studies of Dubos and his collaborators of the Rockefeller Institute. Dubos and Avery[2] found in certain sporulating soil bacilli a soluble enzyme capable of decomposing the specific polysaccharid of the Type III pneumococcus *in vitro*, and then Avery and Dubos[3] protected mice with this material against one million times the fatal dose of this organism. They showed that the mechanism of protection, however, was not that of the destruction of the bacterial cell, but the removal of the capsular armor of the pneumococcus, which was then swallowed up by the phagocytes. The next step was the discovery of microorganisms which would attack the living cell of unrelated species[1] and the isolation of the responsible chemical principles which could be utilized as bactericidal or bacteriostatic agents.

The name tyrothricin was applied by Hotchkiss and Dubos[4] in

* Read November 20, 1942 in the Friday Afternoon Lecture Series of The New York Academy of Medicine.

1940 to an alcohol-soluble and water-insoluble fraction obtained from a culture of certain aerobic sporulating bacilli found in soil. It possesses strong bactericidal properties for many organisms, both Gram-positive and Gram-negative, *in vitro*. It is, however, not a pure substance, and from it there have been separated out two crystalline materials, tyrocidine and gramicidin.[5] Both of these substances are essentially polypeptides, consisting in part of d-amino acids. They are soluble in alcohol and insoluble in water. They show, however, differences in chemical composition, and important differences in their biological characteristics.

Tyrocidine is relatively non-specific. It is anti-bacterial for both Gram-positive and Gram-negative organisms. It behaves like other well-known antiseptics such as metals and chlorine compounds. It is a general protoplasmic poison. It destroys the metabolic activity of the cell; it diminishes its oxygen uptake. It destroys the morphology of the cell and leads, with few exceptions, to lysis of the bacterial cell. These are characteristics of general antiseptics and, like them, its bactericidal properties are inhibited to a marked degree in the presence of tissue extract and serum. This inhibition for tyrocidine occurs to a greater degree against Gram-negative organisms. When organisms are suspended in peptone solution, the inhibition is so marked that it is difficult to demonstrate any effect of tyrocidine on Gram-negative bacilli. Tyrocidine is essentially ineffective *in vivo*, although some protective action was obtained against a pneumococcus infection in the mouse.

The mechanism of action of gramicidin is different. This compound does not act like a general protoplasmic poison. It does not interfere with the oxygen uptake of the bacterial cell. It leaves the morphology of the cell intact. For some time after the cell loses its growth capacity, it still retains its staining characteristics. It is essentially a bacteriostatic agent, and there is evidence that by suitable means its effect upon bacteria may be reversible. It loses very little of its activity in the presence of animal tissues like peptones or serum. Its bacteriostatic effect is highly specific for Gram-positive organisms, although some quantitative differences are shown by different strains. It is highly effective against pneumococci, streptococci, staphylococci, diphtheria bacilli and others belonging to the Gram-positive group. Meningococci and gonococci, although Gram-negative, are somewhat susceptible to gramicidin. It has no effect, however, on Gram-negative bacilli.

Gramicidin is without bacteriostatic effect by intravenous, intramuscular, or subcutaneous injection. The reason for the absence of effect when it enters the circulation is not known. It has been suggested that it may be due to the fact that it is so highly insoluble, or there may be substances in the body, yet unknown, which inhibit its effect.

Experiments in animals and man indicate that it is highly effective against infections by local application. An intraperitoneal injection of 0.002 mg. of gramicidin protects the mouse against 10,000 fatal doses of the pneumococcus. This is, of course, essentially a local action, since no protection is conferred by the intravenous injection of the drug. In this type of experiment, it is from 25 to 50 times as potent as tyrocidine.

Both tyrocidine and gramicidin are toxic in animals. The fatal dose for gramicidin in mice is approximately 12 mg. per kg., and for tyrocidine approximately 80 mg. per kg. The bacteriostatic action, however, involves amounts which are very far below the range of toxic doses.

Gramicidin has been put to use in studies of human infections, in patients with ulcers of the skin, skin infections, mastoids, empyema, osteomyelitis, and other conditions. It is applied locally. The application of 10 mg. of gramicidin, for example, to a staphylococcus ulcer of the leg, results in complete sterilization of the area and signs of healing in twenty-four hours. A dose of 20 to 70 mg. placed into the mastoid cavity has yielded striking clearance of the infection. It has been placed within the empyema cavity of hemolytic streptococcus infections, with some rather dramatic results, but it may be readily realized how difficult it is completely to sterilize such areas, in view of the fact that the compound produces its effect by local action, and the area that is to be disinfected must be readily accessible.

It is obvious that the therapeutic applications of gramicidin are limited. It is not particularly valuable in mixed infections. It is only useful against Gram-positive organisms, and there is some indication that the presence of Gram-negative organisms exerts an inhibiting effect on gramicidin. It is of relatively little value where the circulation is poor, and where sinus formation is present. It may be noted, however, that most war wounds are caused by Gram-positive organisms[6] and, in conditions in which the wound can be fully exposed to the antibacterial agent, the limited experience that now exists indicates, that gramicidin is a chemotherapeutic agent of some promise.

In 1929 Fleming[7] described an antibacterial substance liberated by

a culture of a mould closely related to the Penicillium notatum, which he called penicillin. This material has been extensively studied more recently by a British group at Oxford,[8] and others.[9]

The chemical constitution of this material is not yet known. It is not a pure substance. It is fairly stable. It is freely soluble in water. The potency of the material elaborated by the mould varies with the conditions under which it is cultivated. They have now produced a product which is a thousand times as strong as the original material used by Fleming. For purposes of comparison in study, it is assayed for its bactericidal power by comparison with an arbitrarily chosen standard penicillin. In therapeutic tests they used a penicillin which possesses about 40 to 50 units per mg. of the powder, and dosage is usually expressed in these units.

Penicillin is destroyed in acid solutions, and therefore is not suitable for oral administration. It has, however, been introduced directly into the duodenum in man, with evidence of considerable absorption over a period of several hours. It is highly effective by intravenous injection. It is less effective by intramuscular injection, and least effective by subcutaneous administration. Its toxicity is very low. An intravenous injection of 400 mg. per kg. (about 16,000 units) causes no toxic effects in mice. An intravenous dose of 15 mg. per kg., equivalent to about 50,000 units for a man, causes no effect on the blood pressure or respiration of cats, although perfusion of the cat's heart with 1:5,000 solution gives rise to some depression which is reversible. A single intravenous injection of 200 mg. (about 10,000 units) in man is also without toxic effects.

It is fairly rapidly excreted, apparently chiefly by the kidneys. About half of an intravenous injection appears in the urine in a few hours, and only traces are present in 6 to 8 hours. A large part of the amount found in the urine may be recovered in a purified form as the active material. It appears that some of it is inactivated in the body, although the mechanism is not known. Tissue slices do not seem to destroy it.

Its antibacterial action is very high, and many pathogenic organisms cease growing *in vitro* with a dilution of one part in one million. Under similar conditions, its antibacterial action has been found to be as much as 300 times as potent as sulfapyridine or sulfathiazole. In tissue culture medium it appears to have the same order of activity as gramicidin against Gram-positive cocci.[10] It inhibits the growth of the staphylococcus, streptococcus, gonococcus, meningococcus and others. It does not

appear to be effective against the Bacillus coli, proteus, or influenzae.

Like gramicidin and the sulfonamides, it does not act in the manner of an antiseptic agent, since it does not interfere with oxygen uptake of organisms even in a concentration of 1:1,000. In some specific way it interferes with the growth of bacteria, but does not destroy them. For example, even after the incubation of the staphylococcus in a 1:1,000 solution of penicillin, it will resume its growth readily in subculture, which signifies that the drug is bacteriostatic, although there are conditions under which it may kill the organism.[11] In this respect it resembles the sulfonamide drugs.

In animal experiments it has been found highly effective against staphylococcal and streptococcal infections, and also against infections with anaerobic organisms of gas gangrene.

It is noteworthy that penicillin does not affect leukocytes except in very high concentrations, greater than 1:500. In this regard it is more favorable than most of the locally acting antiseptics, since the leukocytes are known to play an important role in the control of infection.

Penicillin has been used in several experimental studies in man. In staphylococcus bacteriemia, in osteomyelitis, in empyema, in pneumococcic meningitis, and in other infections, some striking results have been obtained. Thus far it seems to have failed in bacterial endocarditis. In bacteriemias and septicemias the blood may be cleared of organisms within two to three days after very large doses such as 100,000 units a day. The most effective mode of administration at the present time is by intravenous injection of several thousand units every few hours. It has also been applied locally to superficial infections, infections of the eye, in a 1:5,000 solution.

Penicillin is still in the experimental stage. It is difficult to produce it on a large scale. Its biological properties and the preliminary results suggest interesting possibilities for this compound, both as a local and as a systemic chemotherapeutic agent.

Sulphamethazine: Among the new sulfonamides, I wish first to speak briefly about sulphamethazine. It was prepared in Great Britain, and the first report of its clinical use was made in May, 1942 by Macartney and his collaborators,[12] of Manchester. It is a dimethyl sulfadiazine. The two methyl groups take the place of two hydrogens on the pyrimidine radical. It is a pale yellow crystalline material. Its bacteriostatic effects lie in the same range as those of sulfadiazine. Its speed of absorption and

of elimination are essentially similar to those of sulfadiazine. The absorption is apparently not complete because the total recovery in the urine is only about 50 per cent of the dose or less, also similar to sulfadiazine.[13] It has the advantage of high solubility. Whereas sulfadiazine is soluble to the extent of 18 to 51 mg. per 100 cc. of water at 37° C., in the pH range of from 5.5 to 7.5, the new compound under similar conditions has a solubility of from 191 to 297 mg., thus about 10 times as soluble in the acid range and about 6 times as soluble in the alkaline range. The acetylated sulphamethazine is nearly 5 times as soluble as the acetylated sulfadiazine in the acid range but, strangely, somewhat less soluble than the acetylated sulfadiazine in the alkaline range, namely, 176 mg. against 248 mg. per 100 cc. When given in amounts of 4 grams as the initial dose and 2 grams every 6 hours, an average blood level of 6 mg. is reached. Conjugation in the blood stream does not seem to be very active and at the higher blood levels amounts only to about 10 or 15 per cent of the total. The sodium salt of this compound is very soluble and 1 gram may be injected intravenously in 3 cc. of solution without reactions. The concentration of the drug in the cerebrospinal fluid is fairly high, some 50 to 80 per cent of that in the blood. Macartney and his co-workers used the drug successfully in pneumonia, meningitis and gonorrhea. The toxic effects were few, mild nausea and vomiting, which sometimes disappeared while the drug was continued. The most important point seems to be that there were no crystals in the urine, even though the concentration of the drug in the urine rose to very high levels. In view of the fact that a significant increase of non-protein nitrogen in the blood occurs in approximately 1 per cent of the cases with sulfadiazine,[14] the new compound is of particular importance. There has been relatively little experience with sulphamethazine, but the indications are promising that there may here be a compound with the high efficiency of sulfadiazine and, because of its high solubility, relatively free of the action which is a source of some of the most troublesome toxic effects, namely, those due to renal irritation and obstruction.

Sterilization of Intestine: During the past two years interest has developed in the possibility of sterilizing the bowel by the local action of the sulfonamides. For this purpose it was necessary to secure a potent soluble sulfonamide, the action of which would be largely confined to the gastrointestinal tract. Up to the present time complete sterilization of the bowel has not been achieved, but interesting advances in that

direction have taken place.

Sulfaguanidine was the first agent belonging to this group which was actively studied. Its synthesis and physical properties were described in 1940 by Roblin and his collaborators.[15] Its pharmacology, antibacterial actions, toxicology, and therapeutic uses have since been studied by several workers.[16]

Sulfaguanidine is soluble in water at body temperature to the extent of approximately 0.2 per cent. Its absorption from the intestinal tract is fairly slow, and its excretion is rapid. It appears to be conjugated to a considerable extent, somewhat more than sulfapyridine, but the conjugated form of sulfaguanidine is more soluble both in water and in urine than that of sulfapyridine. This favors a lesser tendency to precipitation in the kidney. From *in vitro* and *in vivo* studies of its antibacterial activity, it stands among the more potent sulfonamide compounds.

The property of high solubility and poor absorption, as well as rapid excretion, suggested its use in the treatment of intestinal infections such as dysentery, cholera, typhoid, and in the sterilization of the intestinal tract for operations on the bowel. Some success has been attained in the treatment of bacillary dysentery.[17,18] The stools were cleared of the Flexner bacillus by this drug in a group of dysentery carriers.[19] After a daily dose of 4 grams for a week, a total of 28 grams, to a series of patients in one epidemic, the Flexner bacillus disappeared from the stools fairly promptly, by comparison with the results in a similar epidemic which served as a control.[20] It has been used with some apparent success[21] in surgery of the large bowel prior to operation; primary healing in cases that usually run a more stormy course; recovery in some cases in which infection would ordinarily prove fatal; marked reduction in the concentration of coliform bacteria in the feces. Large doses were used, of the order of about 3 grams every 8 hours for several days. The experience with this drug has turned out to be, however, quite variable.[22] Sulfaguanidine has proved to be far from a safe drug. Although in most cases the sulfonamide level in the blood rises only to about 2 to 4 mg., there are others in which it may rise as high as 7 mg. per cent. A number of toxic symptoms similar to those for other sulfonamides have also been observed, namely, nausea and vomiting, headaches, drug fever, conjunctivitis, hemolytic anemia, oliguria and hematuria.

In connection with the use of sulfaguanidine for reducing the population of coliform bacteria in the intestine, the observations of Macken-

zie et al.[23] are of great interest. They, as well as others, found that sulfaguanidine inhibits the growth of laboratory animals (mice and rats). They further found that even in those periods when the rate of growth was normal, the thyroid gland showed hyperplasia, hyperemia, and hypertrophy. It grew, in some animals, to from 3 to 8 times as large. Animals (rats) also developed bleeding from the eyes. These effects were prevented by simultaneous feeding of p-amino benzoic acid and yeast. They pointed out that this phenomenon results from the fact that the organisms of the bowel play a part in the synthesis of essential nutrients, and that sulfaguanidine, by destroying these organisms, gives rise to a nutritional deficiency. To what extent this factor may operate in humans is unknown, but a potential source of trouble is suggested.

Sulfaguanidine does not appear to be quite as favorable a drug for intestinal sterilization as the latest member of this group, namely, *succinyl sulfathiazole* (sulfasuxidine). The synthesis of this compound was described by Moore and Miller[24] in 1942. Succinyl sulfathiazole is not very soluble in water, about 70 mg. per 100 cc. at body temperature, but when dissolved with sodium bicarbonate it forms a sodium salt which is very soluble, and 50 per cent aqueous solutions can be readily made. It is one of the most innocuous of all the common sulfonamides.[25] A daily oral dose of 1 gram per kg., amounting to about 2 ounces for an average man, given for five weeks to a dog produces no appreciable toxic effects, although the coliform count of the feces may fall off from an average of 10 million per gram to less than 100. It is not possible to kill mice with its oral administration. By intraperitoneal injection in mice, the compound suspended in oil or the sodium salt dissolved in water is less than one-tenth as toxic as sulfaguanidine. The drug is very poorly absorbed, since only about 5 per cent is recovered in the urine and large oral doses produce blood levels of only about 3 mg. in the dog and the monkey (1 to 5 grams per kg. per day), less than half of which is in the form of sulfathiazole and the rest in the form of succinyl sulfathiazole. Large doses also appear to be without influence on the growth of rats or the morphology of the thyroid, although in the light of the experience with sulfaguanidine, this requires further study. Essentially similar data have been obtained for the monkey.

This compound forms soluble salts so readily that it is much less likely than other sulfonamides to form crystal deposits in the urine, although there is some evidence that crystal formation may occur.

Striking effects have been reported following the use of succinyl sulfathiazole in intestinal surgery.[26] Doses of 0.5 gram per kg. (about 35 grams) during the first day, and about half as much daily divided into 6 fractions at 4-hour intervals, give rise to concentrations of free sulfathiazole in the feces ranging from 85 to 200 mg. per 100 cc. These exercise a strong local bacteriostatic effect. At the end of about a week, in most cases, the therapeutic effects are in evidence, namely, a marked lowering of the coliform count and of other bacteria, as well as changes in the character of the stool. The stool becomes semi-fluid; it assumes a gelatinous appearance and becomes relatively odorless. The reports indicate that the use of this drug makes it possible to eliminate purgation during the pre-operative period, which tends to result in dehydration. Some of the troublesome and dangerous complications of surgery on the bowel seem to be effectively controlled, namely, gaseous distention, abdominal pains, abscess and postoperative peritonitis. It is much too early to evaluate fully the therapeutic uses and disadvantages of succinyl sulfathiazole. However, the properties of this compound, as well as the limited experience, suggest that it may prove to be an adjuvant of some importance in intestinal surgery and in the treatment of intestinal infections.

In the time that remains, I shall bring together a few of the developments of the past year or two relating to the group of sulfonamides as a whole, especially to trace a few of the threads that seem to run through the whole story. For a long time to come, progress in sulfonamide therapy is likely to be gauged not only in terms of new agents, but in terms of better understanding of the behavior and the uses of the older members. What seems to have become an endless succession of drives for different and better compounds followed immediately the discovery of sulfanilamide. The accounts of these activities, quite naturally, lay stress on dissimilarities—how much more effective one member is than another in the treatment of pneumonia or meningitis or some other infection; how much more quickly one is absorbed than another, or more quickly or more slowly eliminated; how much more toxic one is than another, and so forth. That information is, to be sure, of great importance, but it is also one of the most irregular aspects of the path of progress. No sooner, for example, does one report state that sulfacetimide is the most valuable agent in the treatment of urinary infection,[27] when another records experience indicating the probability that the ad-

vantages do not exist.[28] The welter of discordant experience and difference is a source of confusion. I think it helps us find an anchor in therapy if we set our minds on the similarities among these compounds and on some of the differences in their properties and behavior which one may, perhaps, in a practical sense, ignore.

Mode of Action: The mode of antibacterial action of the various sulfonamides appears to be essentially the same. The view that has the most satisfactory support, is that the sulfonamide exerts its bacteriostatic effect by interfering with the function of p-amino benzoic acid in the bacterial cell, or some compounds in the cell with an essentially similar chemical structure. There is some suggestion that it may interfere with the metabolism of the bacterial cell at other points also, as indicated by the antagonism with methionine, and proteose-peptone.[29,30] The concept involving p-amino benzoic acid was suggested by D. D. Woods in 1940.[31] This compound is a member of the B-complex and is apparently an essential part of the enzyme system of certain bacteria. The molecule of sulfonamide appears to be able to occupy the place assigned to p-amino benzoic acid in the cell, but without being able to perform the function assigned to that position. Under these conditions bacteria cease to grow. There are other hypotheses which have already been largely discarded. A similar fate may be in store for this one before the story is fully known.

Dosage: The effective dosages and the plans of administration of the sulfonamides in common use for their systemic effects are, from the experience which has accumulated, essentially identical—sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, and sulphamethazine. The goal should be a maximum concentration in the blood for a few days rather than a prolonged course of smaller doses.[32] A dosage level which does not produce a marked effect in a few days is not likely to prove more successful over a long period of time unless there is impaired excretion which automatically, by cumulation, raises the effective concentration in the blood. For severe infections, the first daily dose is 10 grams for the average adult; 4 grams in the initial dose, and 1 gram every 4 hours day and night. This is followed by 6 grams daily given in a similar manner. This is continued until the temperature is normal, for two to three days. If the temperature does not fall rapidly to normal but settles down to lower levels, the dose may be reduced to 5 grams or 4 grams daily. The decision concerning this change requires judgment of the

various factors in the particular case. The guide to variations from the average plan of dosage is the condition of the patient, the presence or absence of therapeutic or toxic effects. If two days elapse without a therapeutic effect, the blood level should be determined. If it is below 3 or 4 mg., the dose should be increased, or several doses given intravenously.[33] In less severe infections, the doses are smaller. The infections of the urinary tract appear to respond on the whole to smaller doses, 3 to 4 grams daily.[27,28]

There are isolated experiences which indicate that some infections due to resistant types and strains of organisms may require much larger doses, with resulting blood concentrations of sulfonamide away outside the levels which may be attained with any fair degree of safety, levels of the order of 40 or 50 mg. or more, for effective control. I have reference particularly to cases of subacute bacterial endocarditis.[34] It is not often possible to attain such levels without a dangerous degree of renal blockage with the available compounds. In such cases, of course, the danger of the disease and of the drug must be carefully weighed against each other.

With daily doses of 6 grams, patients acquire blood levels of about 10 mg., and with daily doses of 3 grams, levels of about 5 mg. Two patients receiving the same dose of the same drug may show widely different blood levels due to differences in speed and completeness of absorption, and speed of elimination. While there is a general relationship between the therapeutic effectiveness and the blood concentration of the drug, there are so many factors in human infections which influence that relationship, that in one individual with, for example, a pneumococcus pneumonia, a 4 mg. concentration of the drug will produce a satisfactory therapeutic result for which another patient may require a blood concentration twice as high.[33] Not all the factors responsible for this fact are known, but there has accumulated a great deal of experimental data which suggest reasonable explanations. The bacteriostatic power of the sulfonamides depends upon such factors as the quality of the medium in which the organism grows, the temperature, the pH of the medium, the concentration of organisms, the resistance of the strain, and the speed with which the liver acetylates the drug, since the more it is conjugated, the less is its bacteriostatic action. Some or all of these factors may differ from patient to patient.

How often the sulfonamide blood level should be determined in the

course of treatment is a question that cannot be answered in a manner that will apply to every case. If, during the use of the full doses which we have just discussed, the blood concentration is determined after approximately 20 grams, or at the end of the second or the middle of the third day, a great many cases of poisoning will be prevented, since by that time the concentration will reveal whether the patient is one whose tendency it is to accumulate the drug beyond the level of the average individual. This, again, is a rule which will not cover all cases, but helps in a large proportion of them.

There are several pharmacological differences between the members of the sulfonamide group which should theoretically alter the plan of dosage, but the accumulated experience indicates that these factors do not essentially alter the therapeutic results for the different compounds, if the doses and the intervals between them are applied as I have outlined. Nevertheless, these differences need to be kept in mind for the case of special problems that arise. Sulfanilamide and sulfathiazole are rapidly absorbed. A given dose is likely to cause a peak concentration within an hour or less. In the case of sulfapyridine and sulfadiazine, absorption goes on over a period of four to six hours. In the case of the first two, elimination is quite rapid, and within six to eight hours the blood level has fallen off considerably; within twenty-four hours they are almost completely eliminated. In the case of the latter two, elimination proceeds slowly and two to three days elapse before the larger part of the dose is excreted. Cumulation to toxic levels is therefore more likely with these, a fact that needs to be taken into consideration in those cases in which the drug is used over a more protracted period of time.

Toxic Effects: The sulfonamides are potentially dangerous drugs. There are thus far no exceptions. The list of toxic effects is now quite formidable. No bodily system is immune. It is entirely possible that the toxic effects of the sulfonamides are part and parcel of the effects of these drugs on cells, whether they are bacterial or human cells. It is, therefore, conceivable that the mechanism of action which results in the disturbed metabolism of the bacterial cell results in the phenomenon of toxicity in the human cell.[35]

The toxic effects are fairly well known and perhaps do not require detailed discussion, except to refer briefly to the question of what to do when they occur. This matter, of course, cannot be disposed of by the simple statement that if toxic symptoms occur, discontinue the drug.

since such a decision may also be fraught with hazard.

The renal complications are the ones which present the most pressing problems. They are due chiefly to the precipitation of the insoluble compounds, mainly the acetylated form of the drug in the tubules and renal pelvis. The crystals irritate the kidney, giving rise to renal bleeding, and obstruct the production and flow of urine. These crystals are rarely found in the case of sulfanilamide, which is very soluble, but occur in two-thirds of the cases receiving sulfapyridine or sulfathiazole, and in one-twelfth of the cases receiving sulfadiazine.[14,36] The drug should be discontinued if there is a gross hematuria, also if red blood cells appear in the urine. At this point we should recall the need for a careful search for red blood cells before the drug is started, at least as careful as after the drug is given. Red blood cells are often present in the urine of patients requiring sulfonamides. A very helpful sign is obtained from the urine output. A urine output of at least a liter a day should be maintained. If the urine output in relation to the intake begins to fall off and cannot be maintained, injury of the kidneys is taking place which may lead to anuria, several cases of which have been reported. Fluid intake does not need to be restricted in sulfonamide therapy. The idea of restricting fluids in order to secure higher concentrations of the drug has been abandoned even in the treatment of infections of the genito-urinary tract,[37] since it is now the belief that the drug acts mainly before it enters the lumen of the tubular tract.[38]

Alkalinizing the urine tends to diminish the liability to crystal formation. It has been observed[38] that sodium bicarbonate given in doses equal to those of sulfadiazine and sulfathiazole cuts in half the frequency with which crystals are found in the urine. A point which probably has a bearing on the matter is the observation that in water at 37° C., the conjugated sulfadiazine which has a solubility of 25.5 mg. per 100 cc. at pH of 5.5, becomes 10 times as soluble, namely, 248 mg. per 100 cc., at a pH of 7.5. Under the same conditions, the conjugated sulfathiazole increases its solubility by five times.[39] However, the solubility characteristics of chemical agents cannot always be predicted. It is not the same in water as in urine, and not the same in dilute urine as in urine containing larger amounts of other materials.[40]

In the case of blood changes, a fall of the red or white cell count, or hemoglobin is a fairly common toxic effect. There is no choice but to discontinue in the more severe types of poisoning such as hemolytic

anemia or agranulocytosis. The milder changes often present a dilemma. The drug should be discontinued if the white cells fall below 4,000.[37] In this connection it is very disappointing to discover this number of white blood cells after the drug has been given and no control blood count to which it might be related. Every patient receiving sulfonamide should have a blood count at the start. It may be mentioned that a low white cell count at the start is not a contraindication to the use of sulfonamides. Dameshek and Wolfson[41] treated two patients with severe agranulocytosis with large doses of sulfathiazole in the endeavor to control the sepsis, with indications that the drug may have played a part in the recovery which ensued.

Animal experiments[42] indicate that all members of the sulfonamide group are toxic to the central nervous system, although some are less so than others. Sulfanilamide seems to be less toxic than several of its derivatives, including sulfathiazole. The repeated administration of the sulfonamides seems to sensitize the nervous system. The neurotoxic action is more pronounced in disease of the central nervous system. Among the toxic symptoms seen in man are headaches, dizziness, depression, confusion, aphasia, stammering, toxic psychosis, meningeal symptoms, blindness, convulsions, myelitis, and optic neuritis. Peripheral neuritis with sensory and motor disturbances is sometimes seen. Nausea, vomiting and diarrhea are apparently of central origin. When the milder symptoms occur, the course may be interrupted for a few doses, or the size of the dose reduced. In the more severe forms it needs to be discontinued.

Choice: Concerning the choice of sulfonamides for the treatment of any specific infection, opinion is not unanimous. The early observations that pneumonia was not very satisfactorily controlled with sulfanilamide have received support from subsequent experience, and at the present time the pneumococcic infections are treated almost exclusively with the heterocyclic derivatives of sulfanilamide, namely, sulfapyridine, sulfathiazole and sulfadiazine. The results with sulfanilamide in the treatment of gonorrhea have been, on the whole, striking, but the repeated finding of cases of gonorrhea vigorously but unsuccessfully treated with sulfanilamide which were promptly cured by an essentially similar plan of treatment with sulfapyridine[43] suggested that the heterocyclic derivatives might be more efficacious in this disease as well. The observation that gonococci fairly rapidly acquire resistance when exposed to increas-

ing concentrations of sulfanilamide but retain their sensitiveness when treated under the same conditions with sulfathiazole[44] directed attention to the possibility that sulfathiazole may deserve the first place. More recently, a very careful study from the Brady Institute[37] showed that sulfadiazine is probably the most efficacious member of the sulfonamide group in use in this country for the treatment of gonorrhea. A course of treatment with a daily dose of 4 grams for a period of about ten days was found to effect a complete cure in about 95 per cent of the cases. Some of the earlier observations with sulfathiazole suggested that it might be the drug of choice in staphylococcus infections. There seems to be little doubt of its superiority over sulfanilamide, but its position in relation to the other heterocyclic sulfonamides remains to be established. There seems to be some doubt concerning sulfathiazole in any form of meningitis by reason of the fact that little of this drug enters the spinal fluid. This fact does not finally settle the question, however, since the essential action in the control of meningitis may prove to be that of the drug in the circulation rather than in the spinal fluid.

The final word regarding the choice of sulfonamides in the fifty-odd infections in which they are found useful is not yet possible with the available experience. There is, however, competent opinion to the effect that among the sulfonamides in common use in this country at the present time, sulfadiazine serves all the needs of systemic sulfonamide therapy as satisfactorily as any other, surpasses them in some infections and is, by and large, freer of toxic effects.

Drug-fastness: The problem of drug-fastness in relation to the sulfonamides is receiving increasing attention in the past few years.[44-53] Resistance to the sulfonamides seems to be a characteristic of the strain of organism. What factors are responsible for the *natural* resistance of bacteria to these agents are not yet known.

There is another aspect of the problem of resistance, namely, the fact that certain organisms are able to acquire resistance if exposed to sublethal doses of this group of drugs. Among the organisms for which this has been demonstrated are included the pneumococcus, the gonococcus, the staphylococcus, and the Escherichia coli. The acquisition of tolerance by an organism when it is cultivated in a medium in which the concentration of a sulfonamide is progressively increased seems, therefore, to be a fairly general characteristic. It applies not only to bacteria exposed to sublethal concentrations of the drug *in vitro*, but to those similarly ex-

posed *in vivo* in the course of an infection. A very high degree of resistance may be acquired in this way, so that 10 times as much of the drug may be needed subsequently to produce a bacteriostatic effect.[44] The acquired tolerance can be demonstrated not only by the greater concentration of the drug necessary to inhibit its growth in a culture, but by the fact that the drug in the customary doses fails to cure an animal infected with this organism.[53] The drug-fastness may, under certain conditions, develop very rapidly, as soon as three days after the onset of treatment.[47] It may last a year or longer.[49] Not all organisms or strains are capable of acquiring resistance to all sulfonamides. For example, in one series of observations[44] strains of the gonococcus readily acquired a tolerance to sulfanilamide, but were incapable of acquiring a tolerance to sulfathiazole in a similar type of experiment. In some cases, cross-tolerance has been demonstrated. Thus, for example, in one observation in which the staphylococcus of an infected patient had acquired a tolerance to sulfathiazole as the result of treatment with this drug, it was found that the tolerance also extended to sulfapyridine and sulfadiazine.[52] In some cases, however, cross-tolerance does not occur, or occurs only in one direction. In one set of experiments[51] it was shown that the gonococcus which had acquired tolerance to sulfapyridine was also tolerant to sulfanilamide, whereas when the gonococcus had acquired tolerance to sulfanilamide, it remained normally sensitive to sulfapyridine.

The mechanism by which microörganisms exposed to sulfonamides acquire a tolerance to their bacteriostatic action is not known. It may indeed be the same mechanism which is known to apply to other drugs, namely, that exposure of a population of cells to low concentrations of a drug results in the destruction of the most susceptible members and the survival of the fittest.

There are many practical questions which are directly related to the problem of tolerance, but which at the moment can not be answered. If a case of pneumonia or gonorrhea fails to respond to one of the sulfonamides fairly promptly, should one turn to another member of the group in the hope of avoiding the establishment of a tolerant strain which may then fail to respond to others? If so, when should it be done, and to which member of the group should one turn? The matter of dosage bears on this problem. It has been suggested that sulfonamide treatment should be carried out very vigorously and with large doses in order to insure rapid destruction of the organisms,[46] in the hope of avoid-

ing the development of drug-fastness by subeffective concentrations. The widespread use of small doses of sulfonamides in the case of minor infections such as colds, in which no satisfactory proof of value exists, may well serve as a means of cultivating carriers of sulfonamide-resistant strains. The dissemination of strains of organisms which have acquired a fastness to the sulfonamides carries implications of far reaching importance to the public health. Explorations in this field have hardly scratched the surface.

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